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PULMONARY ALVEOLAR MICROLITHIASIS, OR CALCINOSIS OF THE LUNGS*

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PULMONARY alveolar microlithiasis is a rare and extraordinary disease in which microscopic stones are found within the pulmonary alveoli. The lungs, which are heavy and stony hard, cut with the greatest of difficulty. As far as can be determined this disease was first described by Friedreich[1] in 1856; its present name was originally used by Puhr[2] in 1933.

The case presented below is the third to appear in the English language.

CASE REPORT

A 45-year-old Scottish chauffeur was first seen on January 2, 1942, because of abnormal pulmonary shadows on routine x-ray examination of the chest. He had been a chauffeur for 20 years, after which he tested superchargers for airplane engines and assembled breech blocks for large cannon, but never was exposed to dusts of any sort. This work lasted for 2 years. During the latter part of this job routine x-ray examination of the lungs revealed a diffuse bilateral pulmonary lesion because of which he was not allowed to continue his work. He returned to chauffeuring, at which he continued. He claimed no symptoms, had always been in excellent health and admitted to only slight shortness of breath on strenuous exertion.

The past history revealed no illnesses except for a tonsillectomy in 1912 and pneumonia in 1937. Most of his family had had good health till old age; 1 brother had died at 46 of cancer of the liver. There appeared to be no known pulmonary problems in the family.

His marriage of 20 years brought 6 children, but because of domestic strife he had lived for the last 10 years without communication with his wife or children.

Physical examination at the 1st visit showed a short, wiry man, weighing 160 pounds, with a good color and the appearance of excellent health. Supernumerary nipples constituted the only unusual findings. The cardiovascular system appeared normal. The lungs were normal.

The pulse was 66, and the blood pressure 116/78.

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Diagnostic Studies

Examination of the blood disclosed a red-cell count of 5,170,000, with a hemoglobin of 15.20 gm. per 100 cc. (98 per cent by the photoelectric-cell technic), and a white-cell count of 7700, with 71 per cent neutrophils, 19 per cent lymphocytes, 8 per cent monocytes, 2 per cent eosinophils and no basophils. The hematocrit was 46 per cent, and the corrected sedimentation rate 0.45 mm. per minute. The urine was clear with a specific gravity of 1.024 and negative tests for albumin and sugar; the sediment was normal.

On January 30, 1942, x-ray examination of the lungs (Fig. 1) was reported as follows:

> Both lung fields are mottled throughout, with small areas of density that give the films a ground-glass appearance. This mottling is greatest at the lung roots and radiates through the lung fields, being less striking at the tops and bases of both lungs. It has the appearance of minute particles of calcium in the walls of the alveoli. It is practically symmetrical in relation to both lungs. It is not consistent with Boeck's sarcoid.

A Vollmer patch test for tuberculosis was negative.

The sputum was negative for tubercle bacilli by smear on 3 occasions. It was stringy and mucoid, amounting to 15 to 30 cc. per day. On many days there was no sputum at all.

No diagnosis was made at this time. No lymph nodes were available for biopsy. The diagnosis was thought to be diffuse fibrosis or hemosiderosis, but probably not Boeck's sarcoid.

The patient was not seen again for 6 years owing to World War II. On January 13, 1948, his case was reviewed. The interim history had been uneventful, without significant illness, and only a slow but definite increase in shortness of breath and some weakness after exertion. There were sporadic periods of cough and production of stringy, colorless, mucoid sputum.

Physical examination showed no change except in the lungs, where scattered fine rales had appeared posteriorly. The patient's color was good. Slight exertion produced considerable dyspnea, without the appearance of cyanosis.

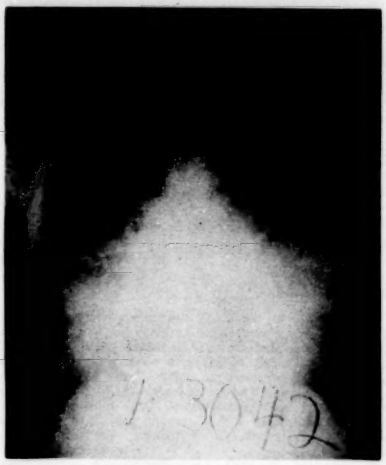
The laboratory findings on January 18 were the same as in 1942.

X-ray studies of the lungs on January 14, 1948, showed some extension and increased density throughout both lungs (Fig. 2).

In October, 1949, after recurrent attacks of severe left-flank pains, a large stone was removed from the left kidney, with uneventful recovery. At about this time a deep cough and sufficient paroxysms to cause vomiting at times developed. The sputum continued to be abundant, clear

and mucoid, and because of this, adenomatosis of the lung was considered as a diagnosis.

On May 6, 1950, bronchoscopy was entirely unrevealing. Cytologic studies produced no diagnostic material, and



JAN. 30, 1942

FIGURE 1. *Bilateral "Ground-Glass" Appearance of Both Lung Fields, with the Minute Particles of Calcium Densely Demarcated in the Lung Structure.*

bronchial washings were negative for tuberculosis by culture and guinea-pig inoculations; cytologic studies demonstrated no cancer cells. Examination of the blood revealed a hemoglobin of 15 gm. per 100 cc. and a white-cell count of 9500, with 58 per cent neutrophils, 22 per cent lymphocytes and 10 per cent eosinophils. The urine was normal except for calcium oxalate crystals in the sediment.

Pulmonary Function

On June 27, 1950, pulmonary-function studies showed nothing remarkable. Ventilatory tests were negative then and again on November 28, with the results presented in Table 1. An x-ray film taken on December 7 disclosed emphysematous blebs at both apexes, more marked on the left (Fig. 3).

Pulmonary-function studies indicated little interference with ventilation or the mass movement of air in and out of the chest. The timed vital capacity, or ability to empty the lungs of 80 to 90 per cent of capacity within 3 seconds, was normal; there was no evidence of obstructive emphysema. Because the vital capacity was low (56 per cent of the predicted value) the air velocity index was higher than normal — a frequent finding with loss of parenchymal tissue unaccompanied by compensatory emphysema. In November the resting alveolar arterial oxygen difference was 34 mm. of mercury compared to a normal of 0 to 10 mm.

Thus, alveolar arterial oxygen difference at rest was 4 times greater than normal, undoubtedly accounting for the extreme physical incapacity on the slightest exertion. The remaining ventilatory studies indicated far better function than had been predicted from the extensive pulmonary damage by x-ray study.

These results are remarkable in that the patient, though quite normal at rest, was now so incapacitated that walking was difficult and dyspnea was considerable with slight exertion. The pulse, with the patient at rest, was 66 to 70, and the blood pressure 130/78. Orthopnea was absent. The weight had fallen gradually from 160 to 128 by the end of November.

After the removal of a large left ureteral stone in 1950 he continued to pass small stones and gravel almost every week and often daily for 5 to 10 days at a time.

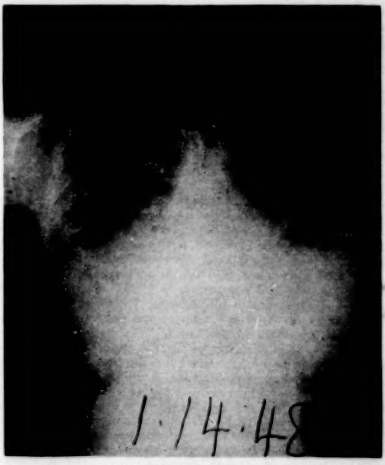
On December 6, 1950, he was hospitalized and received ACTH, 200 mg. a day for 3 days and then 100 mg. daily for 12 days. Improvement was subjective in the sense of well-being, increased appetite and strength and less shortness of breath. There was some gain in weight, but no change in the x-ray appearance of the lungs. Biopsy of the lung was considered contraindicated because of the severe respiratory insufficiency.

An electrocardiogram at this time was consistent with enlargement of the right ventricle and atrium or with cor pulmonale: the PR interval was 0.16 second and the P waves were high, with a QS interval of 0.08 second and right-axis deviation. The tracing disclosed prominent R waves in Leads V_1 to V_6, inverted T waves in Lead V_1 and diphasic T waves in Lead V_2, with a ventricular rate of 77.

A tuberculin test was negative in 1st-strength and 2d-strength purified protein derivative.

On February 7, 1951, urethane, daily in divided doses, was given empirically because the diagnosis was not definitive and in certain granulomatous diseases its beneficial effect has been shown. Thirty days of this therapy had no noticeable effect except for temporary but complete disappearance of the cough and stringy mucoid sputum.

On April 12 cortisone, 100 mg. a day in divided doses, brought the same prompt improvement in appetite, strength and weight gain, with disappearance of cough and sputum, as shown with ACTH during the previous year, but the



JAN. 14, 1948

FIGURE 2. *Progression of the Calcium Deposits (Shown at Autopsy to Be in the Pulmonary Alveoli).*

breathlessness was not relieved. Cortisone was stopped after 48 days, without benefit. The fingers were now somewhat clubbed.

The laboratory findings demonstrated no change, but the urine continued to show calcium oxalate crystals. Physical examination revealed a dull tympany throughout both lungs without evidence of rales. The patient's condition

at rest was good, with a pulse of 70, respirations of 18 and only a slightly dusky hue to the skin.

Metabolic Studies

On October 10 studies were carried out at the Massachusetts General Hospital to ascertain the cause of the urinary stones and gravel, as well as the pulmonary calcium. The urine had a specific gravity of 1.012, with a pH of 6 and a +++ test for albumin, a negative test for sugar and a + test for calcium. The sediment contained 20 to 30 white cells with occasional clumps and 10 to 20 red cells per high-power field; rare spermatozoa and oxalate crystals were noted. Examination of the blood showed a serum protein of 6.5 gm., with an albumin of 3.8 and a globulin of 2.7 gm. (albumin-globulin ratio of 1.4), calcium of 12.2 mg., phosphorus of 3.0 mg. (repeat calcium of 10.4 and phosphorus of 3.2 mg.), alkaline phosphatase of 3.5 Bodansky units and nonprotein nitrogen of 40 mg. per 100 cc.; the serum chloride was 99 milliequiv., and the serum carbon dioxide content 20.4 milliequiv. per liter. Analysis of kidney stone revealed more than 60 per cent ash, no phosphorus, uric acid or cystine and more than 4 per cent oxalate. Smear and culture of a "clean" voided urinary specimen demonstrated no organisms. The Sulkowitch test indicated no elevation of calcium in the urine.

X-ray examination of the abdomen showed calcifications overlying both kidney areas, approximately 7 on each side, the largest being 1 cm. in diameter. A number of the calcifications overlay the region of the renal pelvis. The appearance was consistent with renal stones. The right kidney was somewhat larger than the left. There were also multiple small calcifications in the bony pelvis directly above the symphysis that could have represented stones in the bladder although the appearance was unusual. The extent of these calcifications was greater than that usually found with concretions in the prostate. The bones were of normal texture and density. There was a moderate scoliosis convexity to the left maximum at the level of the third lumbar vertebra.

It was suggested that excessive intake of milk and cheese might have been a factor in the cause of the stones, although here again one would expect them to have contained phosphate. Thus, oxaluria, as the only cause of the stones, did not explain the stones in the prostate. Oxalate crystals were noted in both urinalyses.

TABLE 1. *Pulmonary Function* in June and November, 1950.*

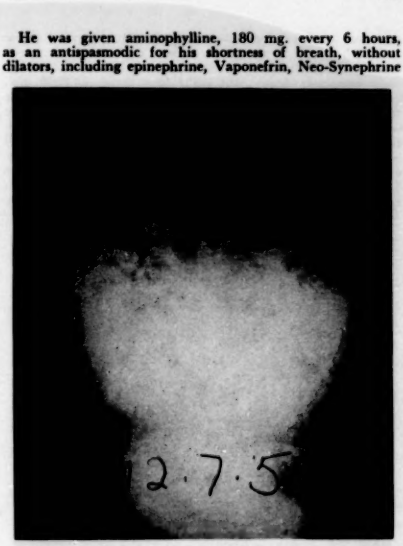
DATE	MAXIMUM BREATHING CAPACITY		VITAL CAPACITY		AIR VELOCITY INDEX	WALKING INDEX
	ACTUAL VALUE	PERCENTAGE OF PREDICTED VALUE	ACTUAL VALUE	PERCENTAGE OF PREDICTED VALUE		
	liters/min.		*cc.*			%
June 27	105	97	2130	56	1.73†	16‡
November 28	98	93	1690	49	1.63†	21‡

*Fluoroscopic study negative on both dates indicated; diaphragm & chest action good.
†High.
‡Normal.

The only suggestions for treatment were a low oxalate diet, with avoidance of milk and cheese, and magnesium by mouth. This regimen had no apparent effect on the tendency to produce renal stones and gravel.

The patient was last seen alive at an office visit on October 20, 1951, when he was much weaker and more dyspneic, with considerable cough and still with stringy clear sputum. Stones were still appearing in the urine every 2 or 3 days, with varying pain, in spite of the low oxalate and the omission of milk and cheese from the diet.

He was given aminophylline, 180 mg. every 6 hours, as an antispasmodic for his shortness of breath, without dilators, including epinephrine, Vaponefrin, Neo-Synephrine



DEC. 7, 1950

FIGURE 3. *Appearance of Emphysematous Blebs at the Left Apex.*

This film was taken ten days after the second series of pulmonary-function studies had shown relatively normal ventilatory results.

and Isuprel for severe dyspnea, but these had proved of little benefit and had been discarded by the patient himself.

At this time he said that he could no longer drive a car and that the slightest exertion produced palpitation, marked shortness of breath and extreme weakness. He had established an antique business at home, requiring almost no physical exertion, but he felt barely able to carry this on.

The final physical examination revealed no noticeable change. The temperature was subnormal. He had lost 24 pounds in weight in a year (to 136 pounds), and clubbing of the fingers was observed with increased cyanosis even at rest. The heart was on the border of enlargement to percussion, and only a soft Grade 2 apical systolic murmur could be heard. The lungs presented the same dull tympany as before, with a few fine, moist rales at the bases after cough. The abdomen was normal, and no organs were felt. There was no sacral or peripheral edema.

The temperature was 96.6°F., the pulse 72, and the respirations 18. The blood pressure was 98/80.

The urine gave a ++ test for albumin, and the sediment was filled with red blood cells and a few white blood cells. This specimen, however, followed the passage of numerous stones with variable pain over the 3 preceding days. X-ray study of the lungs showed no significant change.

On November 12, 1951, the patient died quietly in his sleep at home.

Post-Mortem Examination

At post-mortem examination the body was that of a well developed, fairly well nourished man with cyanosis of the fingernails and lips, clubbing of the fingers, no peripheral edema and a well healed oblique scar in the left flank and lower quadrant. The pleural cavities were almost completely obliterated by dense fibrous adhesions. The pericardial surfaces were smooth and glistening. The heart weighed 480

gm. and disclosed a greatly enlarged right ventricle, whose wall measured 1.5 cm. in thickness. The coronary arteries were patent, without evidence of arteriosclerosis. The lungs were extremely heavy; the right lung weighed 1800 gm., and the left 1500 gm. On removal from the chest cage they retained their shape and did not collapse. The pleurae were thickened by tough, fibrous tissue, and there were multiple minute calcific plaques scattered over the surfaces. All lobes were firm and without crepitus. The apexes bilaterally consisted of large empty cavities, measuring from 6 to 8 cm. in diameter, which were traversed by thick, fibrous trabeculae containing blood vessels. There was no caseation. The lungs cut with great difficulty and with a grating

FIGURE 4. *Anterior View of the Right Lung.*

sound. In all planes the sections were solid and reddish-brown and had the grittiness of sand paper. Multiple, minute calcific concretions were scattered over the surfaces.

The spleen, which weighed 250 gm., was firm and on section showed a prominent follicular pattern. The gastrointestinal tract was not remarkable. The liver weighed 1400 gm.; on section the vascular pattern was greatly accentuated. There were no stones in the gall bladder. The kidneys together weighed 250 gm.; the surfaces were smooth, and there were many small, yellow-tan pebbles measuring 1 or 2 mm. in diameter in all of the calyxes. The ureters were slightly dilated but were patent throughout. The adrenal glands, whose combined weight was 11 gm., were autolyzed. There were no stones in the bladder. The 4 parathyroid glands were identified and appeared to be slightly enlarged. The vertebral bone marrow was red and not remarkable. The head was not examined.

On gross examination the heart was not remarkable.

The gross appearance of the right lung is shown in Figures 4 and 5. Approximately 80 per cent of the alveoli showed pink to blue-pink, laminated concretions within the spaces. In the least involved areas below the apexes the concretions were lying free in the alveoli, without a foreign-body reaction. In these areas the alveolar walls were thin and appeared normal. There were occasional foreign-body giant cells lying free within the alveolar spaces whereas others were in close opposition to the concretions.

In the lower lobes and in the lower parts of the upper lobes the changes were more advanced. In these areas the great majority of the alveoli contained concretions (Fig. 6). There was marked interalveolar fibrosis, and the alveolar walls blended with the interstitial fibrous tissue. Giant-cell reaction to the concretions was present, most of the giant cells being attenuated and linear and encircling the microliths (Fig. 7). There was a moderate interstitial lymphocytic infiltration, with occasional large foci of lymphocytes adjacent to some of the bronchioles.

A small amount of perivascular hemorrhage was present, with slight hemorrhage into some of the alveoli. Bone formation was not observed in any of the sections. The walls of the apical cavities consisted of fibrous connective tissue in which a few laminated, blue-staining concretions, focal collections of lymphocytes and anthracotic pigment were seen. There was no evidence of tuberculosis.

There was chronic passive congestion of the liver. The histology of the kidneys was poorly preserved, but there was no evidence of either acute or chronic infection. The parathyroid glands showed slight hyperplasia. The mucosa of the stomach was not remarkable.

The results of chemical analysis of a section of lung taken from the right lower lobe were as follows: total solids, 55.3 per cent; moisture content, 44.7 per cent; and ash, 34.4 per cent fresh weight and 62.2 per cent dry weight. Analysis of the ash revealed a trace of silicon dioxide, 38.8 per cent phosphorus pentoxide, 51.8 per cent calcium oxide and 0.1 per cent ferric oxide.* On addition of hydrochloric acid for solution of ash, the sample effervesced considerably, indicating the presence of appreciable numbers of carbonates.

This analysis was comparable with the findings in cases studied by Sharp and Danino,[3] Leicher,[4] Munk,[5] Jona,[6] Bénard et al.,[7] Puhr[2] and Mariani,[8] all of whom found that calcium phosphate was the chief mineral present (some of these authors also reported the presence of carbonates).

DISCUSSION

We have found only 10 other cases of this disease reported in the literature. The histology of the lungs

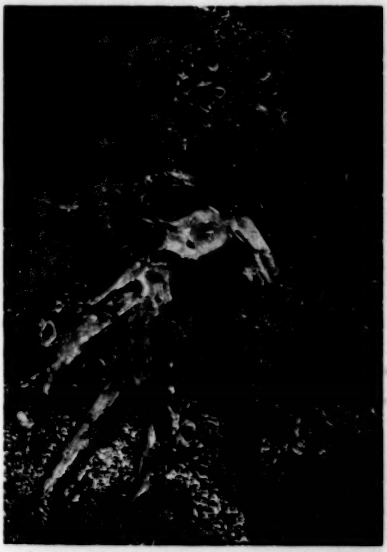


FIGURE 5. *Cross-Section of the Right Lung. Note the reflection of light from the microliths.*

in all 10 cases was the same as that in the case reported above. The pertinent clinical data in these cases are presented in Table 2.

Four patients had healed rheumatic heart disease.

*The iron estimate was not based on spectrophotometer readings, but was roughly estimated from the comparisons of aliquots of 1, 2 and 5 cc. against a 0.1-mg. standard.

Six died in the fourth decade of life, and the average age at death was forty-three years. The sex distribution was not significant, and the occupations in the 11 cases did not provide a clue to the cause.

The case presented above was originally discovered during a routine x-ray examination of the chest at a time when the patient was completely asymptomatic. Over the subsequent nine years of life a slowly progressive dyspnea developed. For most of this time pulmonary-function studies were normal.

During the course of the disease he was seen by many clinicians, and a variety of diagnoses were entertained at one time or another. Calcinosis of the lung was first diagnosed correctly on x-ray study by Dr. Sidney L. Morrison in January, 1942, as "minute particles of calcium deposited in the walls of the alveoli." Other diagnoses were miliary tuberculosis, metastatic carcinoma, adenomatosis and hemosiderosis. But Boeck's sarcoid was never seriously considered. Diseases such as silicosis, histoplasmosis and schistosomiasis can usually be ruled out easily by the history and x-ray pattern. Microlithiasis as a diagnostic name was not considered in this case, and the definitive diagnosis was made after death.

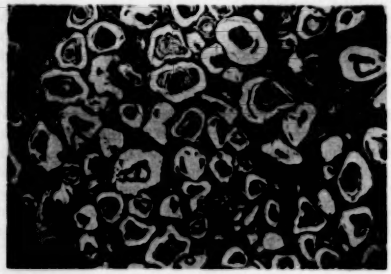


FIGURE 6. *Area of the Lung, Showing Advanced Changes (X25).*

There is complete destruction of the alveolar walls, with marked interalveolar fibrosis. All spaces contain laminated microliths.

Multiple renal stones were passed during life, and pebbles were found in both kidneys at autopsy. Extensive laboratory studies during life were negative.

Etiologic Considerations

This case, like the 10 similar ones, highlights the whole problem of calcium deposition in tissues. Whether the calcium is deposited in cartilage to form bone, in necrotic tissue or in normal tissue, as in the present case, speculations and scientific observations over the years are of great interest. The earliest writers on this subject have made sporadic comments that calcium salts are deposited wherever the body fluids are low in carbon dioxide content and where they are therefore relatively alkaline.

Lazarus and Davidsohn,[11] in 1906, described a case of sarcoma of the skull with marked calcification of the intima of the left atrium, without muscle involvement, that they regarded as being due to lack of carbon dioxide in the arterial blood.

FIGURE 7. *Section of the Lung, Showing Multinucleated Attenuated Giant Cells Encircling a Microlith (X400).*

Hoffmeisten, according to Kuttner,[12] showed that deposits of calcium in the stomach are limited to the interglandular tissue about the upper part of the glands of the fundus of the stomach, where the acid-secreting parietal cells are located. Versé[13] also reported a case of marked calcification of the pulmonary alveolar walls in which the intima of most of

TABLE 2. *Clinical Data in Cases of Microlithiasis Reported in the Literature.*

Source	Age at Death	Sex	Occupation	Healed Right-Sided Heart Disease	Cor Pulmonale	Other Disease
	yr.					
Leicher[4]	44	M	Farmer	No	Yes	
Puhr[2]	49	F	Housewife	No	Yes	Influenza; pneumonia.
Schildknecht[9]	45	F	Housewife	No	Yes	
Jona[8]	29	M	Not given	Yes (mitral stenosis)	Yes(?)	
Munk[3]	35	M	Barber	Yes (mitral & aortic)	?	
Sharp & Danino[7]	52	F	Housewife	Yes (mitral stenosis)	Yes	
Mariani[5]	33	M	Mason for 3 mo.; farmer.	No	Yes	
Bénard et al.[1]	62	M	Not given	No	Yes(?)	
Harbitz[10]	41	F	Housewife	No	Yes	
Friedreich[1]	43	F	Housewife	Yes	Yes	
Present case	45	M	Chauffeur	No	Yes (end stage)	

the left atrium was calcified and the pulmonary veins were heavily calcified with rigid plaques, whereas the pulmonary arteries were free from calcium deposits.

Harbitz,[10] in 1918, stated that calcium deposits in normal lungs, stomach and kidneys were at the common sites of acid elimination. He associated this with glandular abnormalities of the organs of internal secretions such as the parathyroid and thyroid glands. But his case of calcium deposits in the normal tissues of these organs presented no glandular abnormalities. He thought that "some constitutional anomaly or metabolic disturbance of unknown nature" was responsible for this deposit of calcium in normal tissues, especially the lungs, perhaps because of the low acidity of the blood as it released carbon dioxide into the lungs.

In 1913 Schmidt[14] described a case without bone destruction that presented not only extensive calcification of the myocardium of the left ventricle beneath the pericardium but also calcification of the lungs and pulmonary veins, the kidneys, stomach and systemic arteries.

But Wells,[15] in 1911, made the most searching investigation of the whole subject of deposition of calcium salts in cartilage, in necrotic tissue and especially in normal tissues. Briefly, he pointed out that one of the striking features of calcium deposits in human patients is its predilection for the lungs, the stomach and the kidneys when the tissues have not been previously injured or destroyed.

His explanation was that these three organs excrete acids, — carbon dioxide from the lungs, hydrochloric acid from the stomach and acid sodium phosphate from the kidneys, — in consequence of which the parenchymal tissues are relatively alkaline. He showed that the higher the carbon dioxide content of the blood, the higher the concentration of calcium salts in the form of soluble carbonates might be. Thus, the carbon dioxide content of the blood and tissues is important in the absorption, transport and retention of calcium salts, owing to its acidifying capacity. A reduction of carbon dioxide with the appearance of relative alkalinity may cause a deposition of calcium in normal tissues of the lungs. In the stomach wall and in the kidneys calcium deposition may also depend on metabolic changes related to the organ excretion of acids, with resulting local blood and tissue alkalinity, rather than on the presence of diseased tissues.

Wells[16] reported 29 cases of metastatic deposition of calcium in otherwise normal lungs, stomach or kidneys. Twenty-five of these cases were associated with disease of the bones. Only 4 of his cases failed to show causative disease, locally or elsewhere in the body.

In the case reported above, calcium salts were deposited in the alveolar spaces and in the kidneys, with relatively normal parenchyma in each organ. No calcium was found in the stomach wall. Wells also noted that iron salts are insoluble in alkalis and soluble in very weak acids. This observation is in keeping with the chemical analysis of the pulmonary alveolar microliths in this case, which bears out the correctness of Wells's theory.

Wells emphasizes the fact that calcium deposits in cartilage and in necrotic and normal tissue have certain physicochemical properties in common but that physiologic or metabolic alterations in the acid-base relation are most important for the chemical release and precipitation of calcium in all normal tissues seen especially in the lungs, stomach and kidneys as well as in the pulmonary veins. This metabolic concept of calcium deposits in normal tissues offers the soundest explanation for this case of pulmonary alveolar microlithiasis, in which no other endocrine or pathologic condition could be found to account for the calcium deposits in the pulmonary alveoli and in kidneys.

This case presents features that are by no means explained and undoubtedly represent unknown constitutional metabolic abnormalities that fit in with Wells's theory. For, in all living animals, the acid-base alterations of breathing and of gastric and renal acid excretion are common factors of life but in only a few recorded cases does this extraordinary condition of calcium deposits within the alveolar spaces occur.

Whatever the cause of the microlithiasis, there must be an important constitutional variant or a metabolic abnormality in the acid-base and calcium relations as yet not fully understood to produce the alveolar and renal deposits of calcium seen in this case.*

Summary

A case of pulmonary alveolar microlithiasis is presented.

Ten similar cases in the literature that agree generally with the pathological and chemical findings in this case are reviewed.

The pathogenesis of the disease is discussed in detail.

We are indebted to Dr. Fuller Albright, of the Massachusetts General Hospital, for his careful studies of the calcium metabolism in this case, to Dr. Sidney L. Morrison for having been the first one to make the correct diagnosis from his x-ray examination of the lungs in 1942 and to Mr. Frank Stratton, biologic chemist, Boston Police Laboratories, who was responsible for the post-mortem chemical analysis of the lungs. Mr. Leo Goodman, Boston City Hospital, did the photographic reproductions of the x-ray films and pathological sections.

*Since the identification of this case Souman and his associates[17] have found 8 similar cases, which they will present elsewhere.

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POTT'S ABSCESSES IN THE LUMBAR REGION

Treatment by Retroperitoneal Evacuation and Curettage

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THIS report deals with the treatment of 5 patients with Pott's abscesses in the lumbar region. They were treated by retroperitoneal exposure of the abscess, evacuation of the contents and thorough curettage of the abscess wall and the insertion of a strut of iliac bone to prevent collapse of the adjacent vertebral bodies. Three patients were operated on, and all 5 were cared for postoperatively, at Leahi Hospital, Honolulu.

This subject should be of interest to all practicing physicians and surgeons who see patients with low-back pain, because backache is the invariable complaint. The signs and symptoms and even myelographic studies may be identical with those of a patient with a ruptured disk. As pointed out by Beris[1] a laminectomy with such a mistaken diagnosis, even without apparent damage to the dura at the time of evacuation of the abscess, may result in tuberculous meningitis. These patients are quite properly the concern of orthopedic surgeons. My interest in the problem was aroused by the neurologic involvement in Case 1, in which the result appeared so satisfactory that the subsequent patients were referred for treatment.

CASE REPORT

CASE 1. A 63-year-old Filipina was admitted to the staff service of Queen's Hospital with a complaint of pain in the back of 1 year's and weakness of the legs of 6 weeks' duration. She had previously been in another hospital for these complaints, and x-ray examination had shown a destructive lesion of the 3d lumbar vertebra. Extensive studies, including attempted needle biopsy under fluoroscopic control, had failed to establish the etiology.

Physical examination showed a woman who appeared fairly well but was complaining of back pain. There was tenderness over the 3d lumbar spinous process, weakness of the quadriceps muscles and lower legs and absent tendon reflexes in the legs. Sensation was intact. X-ray examination revealed a large osteolytic lesion involving the inferior aspect and corresponding articular surface of the body of the 3d lumbar vertebra, with an associated narrowing of the corresponding intervertebral space (Fig 1). A soft-tissue mass, protruding anterobilaterally from the osteolytic lesion, contained numerous small calcific deposits suggesting Pott's disease. A film of the chest was normal. Lumbar puncture at the lumbosacral interspace showed a partial block. The spinal fluid was clear and colorless and contained 9 lymphocytes per cubic millimeter and a total protein of 500 mg. and a sugar of 123 mg. per 100 cc. The patient had mild diabetes mellitus. She had not improved on conservative treatment, and no diagnosis had been made, so that exploration was advised.

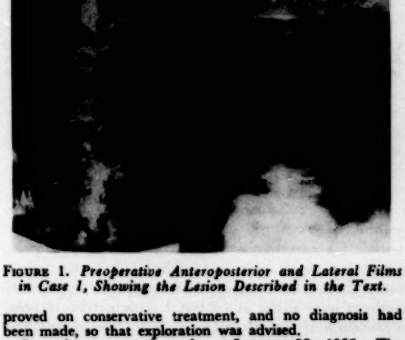

FIGURE 1. *Preoperative Anteroposterior and Lateral Films in Case 1, Showing the Lesion Described in the Text.*

Operation was performed on January 28, 1953. The retroperitoneal space was entered through an oblique incision parallel to and slightly above the left iliac crest. A psoas-muscle abscess was exposed. After the wound had been packed off, the abscess was opened, and a tract leading into the bodies of the 3d and 4th lumbar vertebras identified. The tract was opened, and all diseased bone of the adjacent vertebras removed, including the entire intervening intervertebral disk. The walls of the psoas-muscle abscess were curetted. Slots were then cut in the remaining portions of the vertebral bodies, and a large graft taken from the wing of the ilium inserted to prevent collapse; 1 gm. of streptomycin was placed in the cavity, and the incision closed without drainage. Convalescence was uneventful, and the patient was transferred 7 days after operation to Leahi Hospital, where she received prolonged chemotherapy. An x-ray film taken with a portable machine (Fig.

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2) showed the bone strut in satisfactory position. Three months after evacuation of the abscess, a posterior spinal fusion was performed; she was allowed up 6 months later. Repeated films have shown progressive fusion, and the anterior supporting strut appears to have become fused to

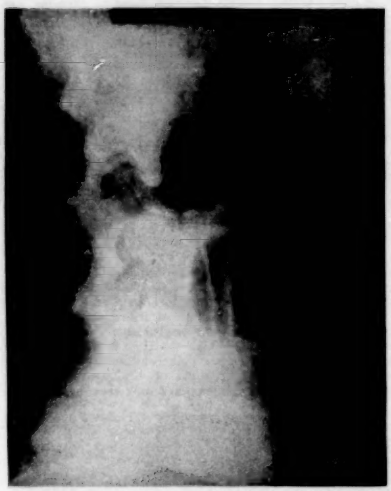

FIGURE 2. *Early Postoperative Film, Taken with a Portable Machine, in Case 1, Showing the Iliac-Bone Strut between the Remaining Portions of the Third and Fourth Lumbar Vertebras.*

the adjacent vertebral bodies. Recent films of the spine are shown in Figure 3.

SUMMARY OF CASES

The ages of the 5 patients in this series varied from seventeen to seventy years (Table 1). Three were females; 2 were males. All complained of back pain, which had been present for three weeks to over a year. Except for tenderness of the spine the physical findings were slight in all but 1 patient who showed weakness and sensory changes. The level of involvement was the third and fourth lumbar vertebras in 4 cases and the fourth and fifth lumbar vertebras in 1. Two patients had active pulmonary tuberculosis; in 1 of these the spinal lesion developed during the hospital course. One patient had had a dorsal spinal fusion for Pott's disease seven years previously. The remaining 2 patients had no other evidence of tuberculosis, and the diagnosis was not established until the time of surgery. Johnson, Hillman and Southwick[2] present a good case for exploring all such lesions because of the frequency of wrong clinical diagnoses and the lack of serious complications from exploration.

OPERATIVE PROCEDURE

With slight modifications the following procedure has been used on all patients:

When psoas-muscle abscesses are present the procedure should be done on the side involved. In all but 1 case operation was performed on the left side. With the patient lying on the right side an oblique incision is made through the skin slightly above the iliac crest. The skin and subcutaneous tissues are then retracted inferiorly, exposing the iliac crest. A single massive graft is taken subperiosteally from the ilium. The fascia and periosteum are closed. The flank musculature and lumbodorsal fascia are then divided about 4 cm. above the iliac crest, and the retroperitoneal space entered.

Retroperitoneal dissection has not been difficult in any patient. Usually, the abscess is obvious and leads one directly to the diseased bone. In 1 patient aspiration through the annulus fibrosus at the suspected level was necessary to find the abscess. The diseased bone, fascia and disk fragments are curetted and débrided thoroughly but not enough to cause generalized oozing. Slots are cut in the anterolateral portions of the vertebral bodies, and with the bodies wedged apart, the single massive

FIGURE 3. *Roentgenogram Taken Two Years after Operation in Case 1.*

bone strut is inserted. A single graft is placed in this position, where it may most quickly pick up a blood supply from the vertebral bodies and adjacent psoas muscle and will not form a sequestrum.

In 1 patient a huge psoas-muscle and retroperitoneal abscess filling the iliac fossa was entered when the fascia over the iliac crest was incised before the bone graft was taken. This incision was therefore simply extended, and the procedure performed through the abscess cavity after it had been evacuated. The abscess cavity extended from the inguinal ligament to the insertion of the psoas muscle at the second lumbar vertebra.

Streptomycin and penicillin are deposited into the curetted cavity. If possible the psoas muscle is sutured over the graft. The abdominal contents are allowed to fall back into their usual position, and the incision is closed in layers without drainage.

TABLE 1. *Classification of Patients.*

CASE	AGE	SEX	SYMPTOMS	DURATION	PHYSICAL FINDINGS	PULMONARY TUBERCULOSIS	SITE OF LESION	PREOPERATIVE DIAGNOSIS
	yr.						*lumbar vertebrae*	
1	63	F	Back pain Weak legs	1 yr. 6 wk.	Atrophy of quadriceps Absent leg reflexes	Absent	3-4	Tuberculosis (?); cancer.
2	58	M	Back pain	1 yr.	None	Active	3-4	Tuberculosis
3	40	M	Back pain	3 wk.	Tenderness of 4th lumbar vertebra; absent ankle jerk on left; limited straight-leg raising.	Active	4-5	Tuberculosis
4	17	F	Back pain; hip pain.	16 mo.	Tenderness of 3d & 4th lumbar vertebras & right lower quadrant	Absent	3-4	Tuberculosis
5	70	F	Back pain	4 mo.	Tenderness of 3d lumbar vertebra; spasm of back.	Absent	3-4	Tuberculosis; cancer.

COMPLICATIONS

The only complication, a fistula, occurred in the patient mentioned above with the huge abscess that was entered at the iliac crest. The fistula closed spontaneously in two months and has not recurred. There have been no recurrences of the psoas-muscle abscesses. No difficulty has been encountered with the ureter, great vessels or abdominal contents. Adhesions have not been found in the retroperitoneal space; the fat there has appeared to be edematous, which has facilitated dissection. Care, of course, has been taken to protect the peritoneum.

FIGURE 4. *Anteroposterior Films before and Two Months after Operation in Case 5.*
The bone strut should be more medial.

POSTOPERATIVE CARE

All patients have been kept on strict bed rest after operation, but turned at will. No particular problems with abdominal distention have been encountered. Patients have all received penicillin and streptomycin for the first week and have then been started on the usual regimen of treatment at Leahi Hospital. This consists usually of streptomycin, 1 gm. every three days for four months, with PAS (para-aminosalicylic acid), usually 12 gm. a day, or INH (isonicotinic acid hydrazide), 5 mg. per kilogram of body weight, or both.

FIGURE 5. *Lateral Film in Case 5.*
The preoperative collapse has been partially reduced by the insertion of the bone strut.

Since there is little experience with this procedure a conservative course has been followed. In all but 1 patient an elective posterior spinal fusion was done two to six months after the anterior procedure. The delay of six months was in a patient with severe pulmonary disease. One patient, eighteen months before retroperitoneal drainage of the abscess, had had a laminectomy at another hospital with a preoperative diagnosis of a ruptured disk confirmed by myelography. At operation a tuberculous abscess was found and drained, and a posterior fusion done. This patient signed himself out of the hospital against advice two months after retroperitoneal drainage of the abscess and the insertion of a bone strut. Appar-

ently, ambulation has not hurt him because, although the present condition of his spine is not known for certain, he is fully ambulant and has not reported to the back clinic.

The co-operative patients have been kept recumbent approximately six months after their posterior fusions. Figure 4 shows the anteroposterior and Figure 5 the lateral films before and after operation in Case 5 (the oldest patient in the series). These were taken before the posterior fusion was performed. The lateral view indicates that the preoperative collapse has been partially reduced. Figure 6 shows the lateral x-ray films before and eleven months after operation in Case 4, and Figure 7 the lateral films before and nineteen months after operation in Case 2. All patients have been ambulatory over six months since operation.

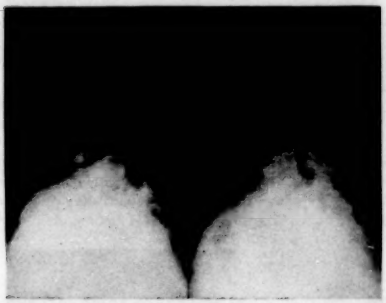

FIGURE 6. *Films in Case 4 before and Eleven Months after Operation.*

DISCUSSION

The advent of antibiotic and chemotherapeutic drugs that inhibit the growth of the tubercle bacillus has considerably altered the indications for surgery in patients with pulmonary tuberculosis. It is probable that indications for surgery in other forms of tuberculosis will be equally affected.

Wilkinson[3] recommends operation on patients with Pott's disease in the lumbar region in whom progressive bone destruction is occurring in spite of full constitutional and antibiotic treatment. Patients without psoas-muscle abscesses are operated on by a posterior transversectomy approach, which probably gives only a limited exposure; my experience indicates that it may be impossible to determine preoperatively if a small psoas-muscle abscess exists.

Bosworth et al.[4] have repeatedly stressed the importance of a solid spinal fusion in the cure of patients with paraplegia. If the bone struts ultimately result in anterior fusions, as they appear to be doing, this object should be accomplished. The insertion of a bone strut in an infected field has obvious disadvantages, but the cleaning out of the infected bone in all patients has left such a large defect in the spine that unless some strut is used, serious collapse and kyphos will certainly occur. If the technic proves safe in larger series it might be argued that the procedure should be done early before possible resistance of the organism to the antibiotic develops.

CONCLUSIONS

Experience with 5 patients indicates that Pott's abscesses in the lumbar region can safely be drained and curetted by the retroperitoneal route without spread of the infection or significant complication provided antibiotic and chemotherapeutic drugs are used. The insertion of a bone strut will prevent collapse of the spine, and to date the bone struts have remained viable and become fused with the adjacent vertebras. Subsequent elective posterior spinal fusion has been used to stabilize the involved spine. It is too early to consider the patients cured, but progressive healing in all patients is encouraging.

FIGURE 7. *Films in Case 2 before and Nineteen Months after Operation.*

I am indebted to Dr. Hastings Walker and the staff of the Leahi Hospital, who treated the patients described in this paper, and to Dr. J. Warren White, consulting orthopedic surgeon, who performed the subsequent posterior spinal fusion.

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FUNCTIONAL EXAMINATION OF THE HEART AT AUTOPSY*

Preliminary Report

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BOSTON

WITH the advent of cardiac catheterization and operative procedures for correction of valvular deformities it has become increasingly important for the pathologist to attempt, from post-mortem examination, a more accurate estimation of the in vivo performance of the heart. The few measurements taken routinely in the past have proved of limited value in the interpretation of cardiac function during life. The present communication reports initial efforts to develop and standardize a procedure of post-mortem valvular examination that can be correlated with in vivo studies of cardiac function. For this purpose resistance to flow through the various heart valves was measured to obtain a quantitative index of the degree of stenosis and regurgitation.

METHOD

The resistance to flow through a valve was determined by measurement of the rate of flow through and the pressure drop across it. A constant head of pressure was ensured by means of a reservoir tank maintained at a constant level seven feet above the specimen (Fig. 1). Flows were varied by partial occlusion of the inflow pipe above the specimen and were calculated by measurement of the volume of fluid that flowed through the valve over a fifteen-second interval. Later in the studies a flow meter was used. Pressures on either side of the valve being studied were measured by means of 3-mm. plastic catheters leading to water manometers. Pressures were referred to the pressure at 0 flow.

In the unopened heart with the pericardium removed the coronary vessels were ligated at their origin. The heart was placed in a water bath at approximately 37°C. To determine stenosis of the mitral valve, a 2-cm. metal cannula was placed into the left atrium through one of the pulmonary veins and tied securely. The remaining pulmonary veins were clamped. One 3-mm. plastic catheter was then placed on each side of the valve, one through the aorta into the left ventricle, and one into the left atrium through the 2-cm. metal cannula. The varying pressures on each side of the valve were then measured at different rates of water flow.

Stenosis of the aortic valve was evaluated in much the same way. The 2-cm. metal cannula with its plastic catheter was placed in the left ventricle through the mitral valve if it was not stenotic or inserted through the wall of the left ventricle if it was stenotic. The tip of the other plastic catheter was positioned in the aorta a few centimeters above the valve. Pressure and flow readings were then taken in a similar manner.

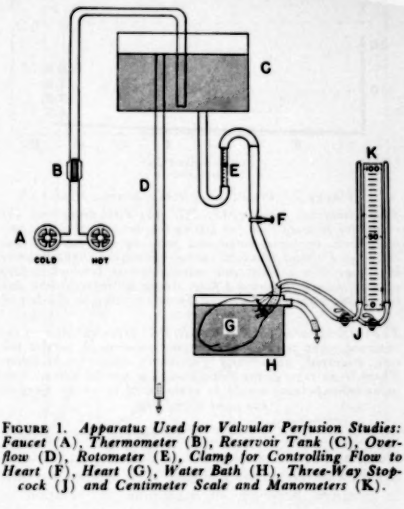

FIGURE 1. *Apparatus Used for Valvular Perfusion Studies: Faucet* (A), *Thermometer* (B), *Reservoir Tank* (C), *Overflow* (D), *Rotometer* (E), *Clamp for Controlling Flow to Heart* (F), *Heart* (G), *Water Bath* (H), *Three-Way Stopcock* (J) *and Centimeter Scale and Manometers* (K).

Regurgitant mitral valves were perfused in a retrograde fashion from the left ventricle. For this purpose a 1-cm. metal cannula with its plastic catheter was inserted into the ventricle through the aortic valve if it was not stenotic, or if it was stenotic the metal cannula was forced through the ventricular wall. The second plastic catheter was placed in the left atrium.

For the evaluation of aortic regurgitation the 2-cm. metal cannula with its plastic catheter was tied into the aorta a few centimeters above the valve. The second catheter was placed in the left ventricle either through the mitral valve or directly through the ventricular wall. To assure a free flow of water the mitral valve was held open by a 2-cm. metal cannula if it was not stenotic. If its opening was small the metal cannula was placed directly through the ventricular wall.

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The tricuspid and pulmonary valves were perfused in identical fashion.

It was decided initially to devise a method as uncomplicated as possible since ultimately it was planned to have it part of the routine post-mortem examination. Therefore, water was used with the

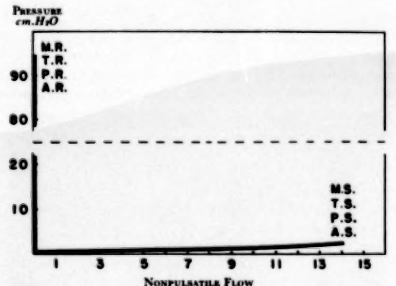

FIGURE 2. *Flow Curves from a Normal Heart.*

The horizontal curve (MS, TS, AS, PS) represents the values for forward flow (or testing for stenosis) through normal mitral, tricuspid, aortic and pulmonary valves. All four valves give almost identical curves. From the slight slope of the curve it is evident that normal valves produce a very mild resistance to forward flow. Increases in resistance due to stenosis would be indicated by curves lying to the left of this curve.

The vertical curve (MR, TR, AR, PR) represents the values obtained when testing for regurgitation through normal mitral, tricuspid, aortic and pulmonary valves respectively. There is no regurgitant flow through a normal valve. Valvular incompetence would be represented by curves lying to the right of this line.

realization that the difference in viscosity between blood and water would lead to difficulty in translating data to the situation during life. Studies are now in progress, however, to determine the relation of viscosity to flow resistance through cardiac valves. These relations cannot be calculated from equations based on laminar flow because blood flow during life is turbulent and because blood is not a homogeneous fluid. A steady rate of flow rather than imitation of the pulsatile flow in life was used in the interests of simplicity and also because the data so obtained were more readily handled mathematically. It is realized that the removal of the pericardium before perfusion may be a source of error, and studies are being carried out to determine the importance of this factor.

Results

Measurements were made on at least three different rates of flow for each valve, and pressure drop across the valve was plotted against rate of flow, yielding a curve for each valve. The slope of these curves represents resistance to flow. The valvular-flow characteristics of various hearts are represented by a family of curves (Fig. 2, 3 and 4).

Data were obtained for each valve in 3 normal hearts, for the tricuspid valve alone in 12 additional normal hearts and then in 11 hearts with valvular lesions. In normal hearts the drop of pressure across the valve was so slight in the direction of usual blood flow that it was barely within the accuracy of the manometer (Fig. 2). Important degrees of stenosis, however, were quite apparent and gave large deviations from the normal pressure drops (Fig. 3 and 4).

There was no regurgitation in the aortic, pulmonary and mitral valves of normal hearts. However, 2 normal hearts without valvular disease showed minimal tricuspid regurgitation. There was no dilatation of the valve ring, and it is impossible to say whether this regurgitation existed in life.

Tricuspid regurgitation of considerable degree in the presence of an anatomically normal tricuspid valve was seen in 7 of 11 hearts with major disease in other valves. In most of these cases of tricuspid

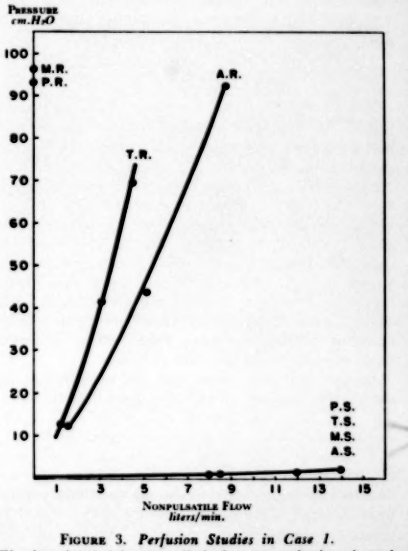

FIGURE 3. *Perfusion Studies in Case 1.*

The functional defects are limited to regurgitation through the tricuspid and aortic valves.

regurgitation the mitral valve was stenotic, and in all cases the tricuspid-valve ring was dilated. The degree of tricuspid regurgitation was unchanged despite manual simulation of systolic myocardial contraction around the ring. It seems probable that these valves were incompetent during life because of the valve-ring dilatation. Three patients with a murmur before death interpreted as being due to mitral regurgitation failed to show mitral regurgitation by per-

fusion but did show tricuspid regurgitation (Fig. 3). It is likely in these cases that the tricuspid regurgitation was responsible for the systolic murmur heard to the left of the sternum. This is illustrated by the following case:

Case Reports

Case 1.* A 54-year-old man without a history of rheumatic fever or syphilis was admitted to the hospital because of progressive exertional dyspnea of 4 years' duration. The heart was enlarged, the border extending to the left 6th interspace in the anterior axillary line. There was a Grade 2 harsh basal systolic murmur, a Grade 3 blowing basal diastolic murmur, loudest along the left sternal border, a Grade 2 apical systolic murmur and a Grade 3 apical diastolic rumbling murmur with a presystolic crescendo.

The blood pressure was 140/50. The clinical diagnoses were rheumatic heart disease with mitral stenosis, mitral regurgitation and aortic stenosis.

At autopsy the heart weighed 465 gm.; the left ventricle was slightly hypertrophied, and the right atrium was dilated to twice the normal size. The mitral, tricuspid and pulmonary valves were structurally normal, although the tricuspid ring was dilated. The aorta showed typical syphilitic changes, with "tree barking" of the intima and dilatation of the ascending portion. The coronary ostia were severely narrowed. The aortic-valve cusps were thickened and widely separated.

On perfusion there was no stenosis of any valve, and the mitral and pulmonary valves were entirely competent. However, there was moderate regurgitation through both the diseased aortic valve and the normal tricuspid valve. It was believed that the dilatation of the tricuspid-valve ring was of such degree as to account for the regurgitation.

In some cases the ante-mortem diagnosis of the valvular lesions agreed qualitatively with the diagnosis made by perfusion, but what was clinically thought to be a valvular lesion of major functional importance proved to be insignificant. This is shown in the following case:

Case 2. A fifty-year-old woman was admitted to the hospital in severe congestive heart failure. At 11 and 16 years of age she had had episodes of acute rheumatic fever, and at the age of 17 the 1st heart murmur was heard. She had been in chronic congestive heart failure for 15 years.

The heart was tremendously enlarged, and murmurs of mitral stenosis, mitral regurgitation, aortic stenosis and aortic regurgitation were heard.

The blood pressure was 110/70. The primary disability was believed due to mitral disease.

At autopsy the heart weighed 600 gm. Both ventricles were slightly hypertrophied; the left atrium was dilated to twice, and the right to 4 times the normal size. All valves showed rheumatic involvement. The mitral valve had a "fish-mouth" configuration, with a rigid, thickened posterior leaflet. The anterior leaflet, although thickened, was flexible, and 2 fingers could easily be inserted into the valve before opening. The tricuspid valve, although its chordae tendineae were considerably shortened and thickened, had a dilated ring and also admitted 2 fingers before opening. The pulmonary valve showed minimal interadherence of 2 commissures. The aortic valve was severely stenotic, with rigid, inflexible cusps that had an ostium of only 5 mm. in greatest dimension before opening.

On perfusion severe aortic stenosis and moderate aortic regurgitation were found. The tricuspid valve showed free regurgitation, but no significant stenosis. There was no significant stenosis of the mitral valve, but backward perfusion through the valve produced a fine, forceful jet, certainly sufficient to cause a loud murmur but of no functional significance. The pulmonary valve was not perfused.

*Previously reported in the Case Records of the Massachusetts General Hospital (Case 41012). *New Eng. J. Med.* 252:32-36, 1955.

Discussion

The extent to which quantitative inferences of in vivo dynamics can be drawn is at present unknown. Further investigation of variables such as viscosity, effect of the pericardium and post-mortem myocardial changes is being carried out. Of considerable interest will be the perfusion of hearts in cases previously studied by cardiac catheterization.

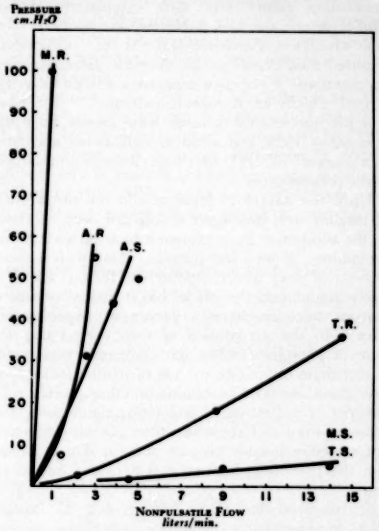

Figure 4. *Perfusion Studies in Case 2.*

There are multiple functional valvular defects in this case. However, there is no significant increase in the resistance to forward flow through the mitral and tricuspid valves. Although there is some mitral regurgitation, it is of minor degree. Marked incompetence of the tricuspid valve, moderate aortic regurgitation and severe aortic stenosis are present.

Summary and Conclusions

Routine morphologic examination of the heart at autopsy has proved to be of limited value in the interpretation of the functional state of the heart during life.

Post-mortem estimation of the degree of stenosis or regurgitation in the heart by measurement of the rate of flow across its valves has been at variance in a number of cases with the clinical evaluation of the valvular mechanics. This suggests that the generally accepted interpretation of certain cardiac murmurs, as originally based on morphologic post-mortem examination, may not be entirely accurate.

LENTE INSULIN IN THE TREATMENT OF DIABETES*

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CHARLTON AND BOSTON, MASSACHUSETTS

HAVING been employed in certain other countries for over two years previously, lente insulin was made available for general use in the United States in August, 1954. One of the first papers describing the results of clinical trials of insulin zinc suspensions came from their originators, Hallas-Møller et al.[1] and was published late in 1952. Not long afterward, Lawrence and Oakley,[2] of London, reported their experience in the early use of the new preparations. Since then numerous articles have appeared, chiefly in European journals.[3-10] We have had the opportunity of using lente insulin since the summer of 1953, first as an investigational and later as a market product.¶ Our experience is summarized in the present paper.

Until the advent of lente insulin the preparation of insulins with prolonged action had been achieved by the addition of basic protein substances such as the protamines, globins and histones, along with a small amount of zinc. The compounds so formed are relatively insoluble at the pH of blood and after subcutaneous injection have a prolonged hypoglycemic effect. In the preparation of these long-acting insulins a phosphate buffer has commonly been used. Under these conditions, the use of small quantities of zinc alone (without protamine or other protein substances) is ineffective in prolonging significantly the action of insulin. Larger quantities are more effective but are objectionable because of local skin irritation and the possibility of toxic action over a period of years.

It remained for Hallas-Møller and his associates[11] to show that if phosphate and citrate are excluded and acetate substituted as the buffer, zinc in low concentrations (0.20 to 0.25 mg. per 100 units of insulin) will combine with insulin to form compounds that at the pH of the blood are relatively insoluble and after subcutaneous injection have a protracted hypoglycemic effect. The superiority of acetate over phosphate or citrate as a buffer lies presumably in a greater affinity of zinc for the latter substances than for insulin. Hallas-Møller et al.[11,12] developed three types of insulin zinc suspensions: insulin semilente, an amorphous preparation with a duration of action of twelve to fourteen hours; insulin ultralente, a crystalline compound with a length of action of well over thirty hours; and insulin lente, a mixture of ultralente and semilente in the proportion of 70:30. The lente insulin available commercially in the United States is similar to the third type. The 70:30 ratio was chosen on the basis of clinical studies to be the one most generally useful since its duration of action is in most patients about twenty-four hours and its effect quite similar to that of isophane (NPH) insulin or a 2:1 mixture of crystalline insulin and protamine zinc insulin.

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From the Elliott P. Joslin Camp, Charlton, Massachusetts, and the Joslin Clinic and the Baker Clinic Research Laboratory, New England Deaconess Hospital, Boston.

Technical assistance was given by the following medical students: Sidney I. Le Bauer (Duke), Edward J. G. Noble (Toronto) and Richard V. Paul (Tufts).

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¶Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

MATERIAL AND METHODS

In the past two years lente insulin has been used by us and our associates in the treatment of over 300 patients. The results reported below were obtained in special studies of 57 diabetic boys attending the Elliott P. Joslin Camp at Charlton, Massachusetts, in 1954 and 43 patients observed at the New England Deaconess Hospital in that year. Both at camp and in the hospital the usual daily program of the subject regarding diet and activity was not disturbed, and in studies comparing the effect of different insulin programs, pains were taken to ensure comparable conditions.

For the most part, capillary blood was used for the determination of blood sugar although with hospitalized patients, for technical reasons, venous blood was taken when fasting samples were desired. The methods of Folin and Malmros[13] and of Folin[14] were used, respectively.

RESULTS

Comparison of Effect of Isophane (NPH) and Lente Insulins

The effect of isophane (NPH) and lente insulins was compared both in day-by-day maintenance studies and in tests involving the determination of the blood sugar at frequent intervals over a twenty-four-hour period. At the summer camp, with diet and physical activity as nearly uniform as possible and with the insulin dose kept at the same level, 57 boys ten to fifteen years of age were maintained for three or more days on lente and then for a comparable period on isophane insulin, or vice versa. The insulin dose ranged from 12 to 68 units daily and in 34 of the boys was 30 units or more daily. The diet ranged from approximately 180 to 225 gm. of carbohydrate, 85 to 120 gm. of protein, 90 to 120 gm. of fat and 1900 to 2500 calories daily. On certain days the blood sugar was determined before each of the three meals and at about two hours after the evening meal. It is evident from the composite values shown

in Figure 1 that there was no significant difference between the degree of control with the two types of insulin. Each resulted in blood sugar values somewhat higher than is desirable for excellent control, but this is a matter of the size of the insulin dose and

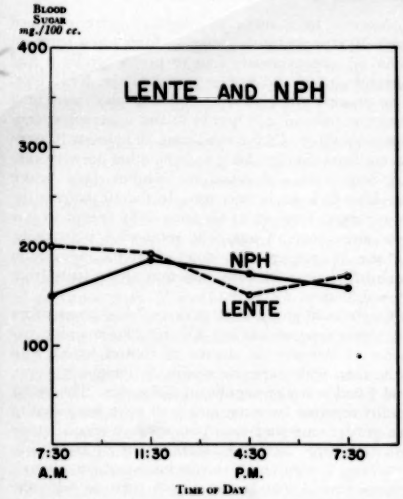

FIGURE 1. *Comparison of the Long-Term Effect of Isophane (NPH) and Lente Insulins, Showing the Average Blood Sugar Values in 57 Diabetic Boys Maintained for Three or More Days First on One and Then on the Other Type of Insulin.*
Usual diets and activity were allowed.

is not directly relevant to the present discussion. Whether the slightly higher fasting value and the lower value at 4:30 p.m. with lente insulin are significant is problematical since our general experience suggests that there is no important difference in duration and intensity of action between lente and isophane insulin.

In addition to these observations based on day-by-day maintenance, studies were carried out to determine the behavior of the blood sugar over a twenty-four-hour period, first on lente and then on isophane insulin and vice versa. During such days the boys were allowed to continue with their usual diet and activity. The insulin dose given was that which was appropriate clinically for the patient at that time. Only single doses of lente or NPH insulin were given, with no addition of crystalline insulin, during the days of study. The blood sugar was determined every two hours throughout the day and night. Since capillary blood obtained from finger-tip or earlobe puncture was used, the quantity of blood necessary was negligible, and the inconvenience to the patient reduced to a minimum. The results are shown in Figure 2.

Each value represents the averages of those of 23 boys. It is obvious that the behavior of the blood sugar was remarkably the same on the two types of insulin despite the fact that the fasting values were somewhat more divergent than one would have liked in an ideal study. There is some indication that the effect of the lente insulin started to diminish two to four hours earlier than that of the NPH type, and this is consistent with the results shown in Figure 1. This finding is of interest in view of the impression of Peck et al.[8] that in certain patients "there was evidence that lente insulin has activity somewhat longer than NPH insulin."

From the data just cited and from other experience in the daily care of patients we believe that the effect of lente insulin is very close to that of the NPH variety. There may be minor differences in certain patients, but, in general, the physician may substitute lente insulin for NPH insulin in similar dosage with no important change in the degree of control obtained.

Addition of Unmodified Insulin to Lente Insulin

In the treatment of diabetes in recent years it has become common practice to prescribe for certain

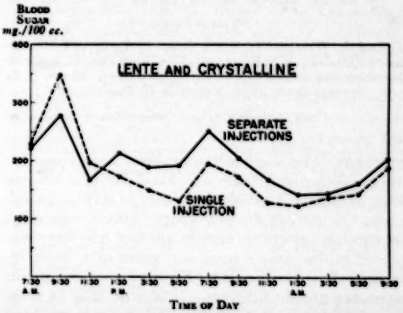

FIGURE 2. *Comparison of the Effect of Identical Doses of Isophane(NPH) and Lente Insulins, Showing the Average Blood Sugar Values in 23 Diabetic Boys after Single Injections of the Two Types of Insulin.*
Usual diets and activity were allowed.

patients a dose, often small, of regular (or crystalline) insulin to be taken along with isophane (NPH) insulin in a single injection daily before breakfast. This has been a most successful plan since, on the one hand, it has assured adequate insulin effect early in the day at a time when isophane insulin is least active and, on the other hand, it has allowed the patient to obtain the benefit of a larger total amount of insulin without increasing the dose of isophane insulin to a

point at which afternoon or evening hypoglycemic reactions are precipitated.

At the time of the introduction of isophane insulin into general use it was shown that this type could be placed in the same syringe with regular (or crystalline) insulin and injected with retention of most of the rapid action of the unmodified type.[15] Quite naturally it became important to determine whether in like manner crystalline insulin may be given in a single injection with lente insulin. Our results in this regard are shown in Figure 3.

In this study 40 boys were given a combination of lente and crystalline insulin in the morning before

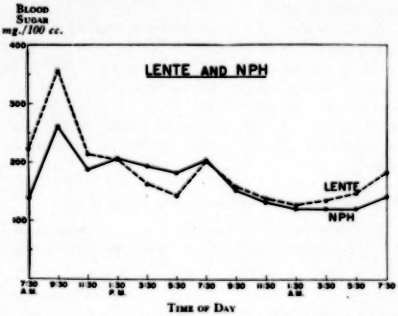

FIGURE 3. *Comparison of the Effect of Lente and Crystalline Insulin Given Subcutaneously on One Day by Separate Injection and on Another in the Same Syringe, Showing the Average Blood Sugar Values in 40 Diabetic Boys.*

Usual diets and activity were allowed.

breakfast. The doses of insulin were those appropriate for the patient concerned. Food and activity were kept as nearly constant from day to day as practicable. On one day the two types of insulin were given by separate injections, and on another day they were placed in the same syringe and given in a single injection. It is obvious from Figure 3 that the results were not greatly different. It is true that at 9:30 a.m., two hours after insulin, the evidence of rapid insulin activity was less with the combined than with separate injections. However, by 11:30 a.m., the difference was relatively small. From then on during the rest of the twenty-four hours a slightly greater hypoglycemic effect was obtained with the combined injection.

These results agree in general with those of Holcomb, Page and Stephens,[16] except that these workers found that for as long as six to eight hours after injection the hypoglycemic effect might be considerably greater when lente and regular insulin were given separately. (It should be noted that Holcomb et al. used regular, whereas we used crystalline, insulin.) From a practical standpoint, in the day-by-day treatment of patients generally, we have found that good results can be obtained if lente and crystalline insulins are given in a single injection just as with isophane and crystalline insulins.

Evaluation by Patients

Answers to a series of questions were obtained from 30 representative patients. After using lente insulin for approximately four to twelve weeks, 4 had discontinued it and had returned to the NPH type. The reasons given were as follows: poor tests in 2 patients; pain on injection in 1; and nonmedical considerations in 1. Of the remaining 26 patients 10 were taking lente insulin alone, and the other 16 were taking both lente and crystalline insulins daily before breakfast in a single injection. In the 10 patients the dose ranged from 16 to 66 units daily except in one boy, seven years of age, who received 4 units daily. In the 16 patients the dose of crystalline insulin varied from 4 to 24 units, and that of the lente from 16 to 120 units.

Of the total group of 30 patients 7 had never taken any other type of insulin. Of the 23 remaining patients 14 thought the degree of control better with lente than with isophane insulin, 5 thought it worse, and 4 had noted no significant difference. The better results reported by some may well have been due to the greater care that most patients in a special study will take with diet and other aspects of treatment. However, it seems safe to conclude that, in general, control was at least as good with lente as with the isophane type.

Three patients noted more frequent or more severe hypoglycemic reactions with lente insulin than with other types of insulin. One reported fewer reactions. Our general experience has been that reactions are neither more nor less common with lente than with isophane insulin.

Four patients reported more, and 1 less, discomfort at the time of injection of lente insulin than with other varieties. This complaint, which has also been made by patients not in the study group, is probably due to the fact that with other types of insulin used in this country, the tricresol used as a preservative acts as a mild local anesthetic. In the lente insulin as now marketed, the preservative is methylparaben, which is not anesthetic.

Most patients described no local allergic response to lente insulin even though, as in 4 patients, such untoward effects were seen with other insulins. However, allergic responses to lente insulin occur in certain patients. One reported "slight redness and swelling," and another "at times, itching and small hives." Holcomb, Page and Stephens[16] presented a case of allergy to lente insulin, and Beaser[17] "encountered a patient in whom generalized urticaria developed on lente (Lilly, 70/30 mixture) insulin." Venning[6] noted local allergic reactions, as did Cobley and his co-workers,[18] who observed local sensitivity in 7 pa-

tients, of severe degree in 1. However, Gurling et al.[10] reported that in 479 patients "local reactions were never bad enough to cause cessation of treatment."

Discussion

If, as our studies and general experience indicate, lente and isophane insulin act similarly, why have both of them on the market? Why add another insulin to the growing list that now, in the United States, includes six varieties? Has lente insulin any special advantages?

The chief merit of lente insulin over other modified types is that it is a simpler product, containing no added protein such as protamine or globin. One might anticipate fewer allergic responses to it, and that seems, indeed, to be so although they do occur. Sufficient time has not elapsed to make a statement regarding frequency of atrophies of subcutaneous fat. In our experience fat atrophies have followed the use of all other types of insulin[19] in susceptible persons and their occurrence with lente insulin would not be surprising. Indeed, 1 case has been reported by Peck and his associates.[8]

A theoretical advantage of lente insulin should be mentioned. Containing no protamine, it cannot, over a long period, have any deleterious effect on blood lipids that might come from protamine, a heparin antagonist. This consideration has admittedly no basis in demonstrated fact.

It is likely that if approximately twenty years ago the method of preparing lente insulin had been known, one would not have seen the development of protamine zinc, globin and isophane insulins. Since, however, lente appeared relatively late, the modified insulins now available will undoubtedly be used for a long time to come. In time, the number of insulins should be reduced rather than multiplied in the interests of simplicity and safety for the patient. Our own policy at the moment is not to shift patients from the insulin program that they are following, provided they are doing well. With new patients, with those prone to allergy to other types of insulin and with those having difficulty in maintaining control with the insulin they are now using, trial of the lente type deserves consideration.

It is important to emphasize that all varieties of insulin are effective if used in proper dosage and at the proper time during the day in relation to food, activity and the natural behavior of the blood sugar of the individual patient. It is the responsibility of the physician to plan treatment so that, with the patient on a truly adequate diet, the blood sugar may be kept as nearly normal as possible throughout the twenty-four hours without frequent or severe insulin reactions. Only in this way can the best possible health be assured the patient, not only now but also in the distant future.

Summary and Conclusions

Special studies and general clinical experience with lente insulin are reported.

Lente insulin has a prolonged hypoglycemic effect, with a duration of action of approximately twenty-four hours. Its action closely resembles that of isophane (NPH) insulin, and the two types may, in general, be used interchangeably.

Crystalline insulin may be given in a single injection with lente insulin just as with NPH insulin, with preservation of most of the rapid action of the unmodified type. This procedure is practicable and effective from a clinical standpoint.

A few patients, particularly children, may complain of discomfort at the site of injection that is greater than that with other types of insulin. This is presumably due to a difference in the type of preservative used in the preparation of the insulins for the market.

Allergy to lente insulin does occur, but experience to date suggests that it is less frequent than that to other varieties.

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MEDICAL PROGRESS

TREATMENT OF MIGRAINE

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BOSTON

IN 1933 Critchley[1] made the following remarks before the Harveian Society:

> Migraine has been the happy hunting ground of the theorist, and the problem has been attacked by representatives of all branches of medicine. Each in turn has discovered in migraine phenomena pertaining to his own specialty — has hit upon the true nature of the malady — has found the infallible remedy. Obviously, such mutually exclusive viewpoints cannot all be entirely correct, and the multiplicity and diversity of the hypotheses suggest that the problem is more complex than imagined, and probably one which presents a number of facets.

In spite of industrious and imaginative research and a wealth of medical observation and literature since that time, this statement of the case still seems valid for 1955. Much has been learned regarding the mechanism of migraine, linking it to misbehavior of the cranial vessels, but the fundamental factors that cause this misbehavior remain a mystery. Many new approaches to the problem of treatment have been made, but no single specific remedy has been found that bears the test of time in all cases. The status of knowledge of migraine may be compared to the understanding of diabetes when it was first recognized that diabetes is characterized by the presence of excess sugar in the urine and blood. This constant physiologic aberration in diabetes is comparable to the consistent finding of a disturbed state of the cranial vessels in migraine. The establishment of a fuller concept, such as has come about in diabetes through discovery of the role of the pancreas, its interrelations with other physiologic systems and the isolation of its hormone, still lies ahead for migraine.

Inconsistencies in the reported results of treatment for migraine are prevalent for many reasons:

Although migraine may well prove to have a common fundamental mechanism the "trigger factors" that set it in operation probably vary from patient to patient.

Remissions and exacerbations of the severity and frequency of migraine occur "spontaneously," or in relation to changing life situations, weather, locale, illness, operations, vacations, work, moods and economic status, with the result that concurrent medical therapy may receive credit or blame that is not its due.

Migraine is notorious for responding temporarily to any new and encouraging form of therapy and is greatly influenced by the doctor-patient relation. Friedman and von Storch,[2] in one of the few controlled studies, have shown that 24 per cent of patients are relieved by placebos. Forms of therapy that require hospitalization or frequent visits to the doctor's office for injections may well derive much of their seeming value from personal contact and attention and other psychogenic influences. The reassurance derived by the patient from consultation with a specialist may be as important as the medicine that the specialist prescribes.

There has been a great tendency for investigators in this field to present results of studies in which several forms of therapy are employed at once and yet conclusions are drawn about only one. Other reports lack detailed, objective records of the frequency and severity of attacks before, and even after, treatment was started. In many studies the patients have been observed over a period that is insufficient to allow for the effects of the natural variations of the disease. Prolonged periods of accurately recorded observation of the patient under normal living conditions, both before and after the use of a single therapeutic weapon, and the use of the "double-blindfold" technic, in which neither doctor nor patient knows the nature of the test preparation, might well be applied to studies of migraine therapy more often.

There is confusion and dissension among authors regarding which headaches are to be included within the diagnosis of migraine.

Thus, it may readily be seen that, although the practicing physician may well be justified in using all the means at hand to help his patient, such as combinations of painkillers, vasoconstrictors, sedatives, hormones and psychotherapy, he must be extremely careful and critical, when he assumes the role of an investigator, in his reported evaluation of the specific effect of any one agent on migraine. Bearing in mind that very few published studies of the treatment of migraine have taken these facts into consideration, one may approach the subject of current forms of therapy. One must also remember that, uncontrolled as many observations have been, they have in many cases contributed valuable suggestions for combating this elusive malady.

DIAGNOSIS

The diagnosis of a disease becomes more definite in proportion to knowledge of its clinical picture, natural history, pathologic physiology and tissue pathology. In migraine no specific tissue abnormality

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has as yet been observed grossly or under the microscope, and only the surface mechanisms of its pathologic physiology have been discovered. Consequently, there is still room for a good deal of divergence of opinion about what migraine is.

Many human maladies are characterized by recurrent episodic aberrations of physiologic processes. Among these might be numbered gout, periodic disease, angioneurotic edema, asthma, epilepsy and migraine. These conditions have several characteristics in common — namely, relatively short episodic occurrences and recurrences, self-limitation of episodes, tendency at times to change into a "status condition," a positive family history and evidence of both local and general physiologic disturbances. Other conditions might be listed that show several but not all of these tendencies (hemolytic anemia, paroxysmal hemoglobinuria, cardiac arrhythmias, various allergic disturbances, familial periodic paralysis and so forth). Thus, migraine appears as one among a group of episodic physiologic disturbances that have a number of characteristics in common. The various entities within this group are further identified by the clinical descriptions of the episodes; their natural history; their specific local and general physiologic aberrations, some of which are demonstrable clinically or by laboratory tests; and the exclusion of organic causes for a similar set of clinical symptoms. When these principles are applied to migraine, some cases always fulfill all the standard criteria, and the diagnosis seems unquestioned. Others meet these diagnostic standards only in part or only at times, manifesting at other times symptoms that are related to migraine only because they are episodic disorders occurring in a known migraine sufferer. Still others present a clinical picture and natural history unlike migraine, but nevertheless exhibit certain features of pathologic physiology that are similar to those known to take place in migraine, and because of this may be related to the general genus of migrainous disorders.

Clinical Description

The most characteristic symptom of migraine is the sudden occurrence of a visual scotoma, often embellished at its edges with zig-zag lights ("fortification spectra") spreading slowly over one or, at times, both visual fields and disappearing usually within the course of a few minutes to an hour. Repeated occurrences of this type, in a person in whom no other cause may be demonstrated, supply sufficient grounds to make the diagnosis of migraine. This phenomenon at other times or in other persons may be represented by other bizarre neurologic fireworks, such as aphasia, alexia, vertigo, hemiparesthesia, inability to concentrate and lack of memory and judgment. In most such cases headache follows the neurologic disturbance, but in some it may not be recorded by the patient. Usually, severe headache is present for several hours and is accompanied by nausea, vomiting and prostration. Such an attack would be accepted by all authors as representative of "classic" migraine. Some patients have this sort of attack and only this sort throughout their "headache years." In their families, however, one is apt to discover close relatives who have never, or very rarely, suffered this "classic" attack but who have had frequent recurrences of plain "sick headache," in which there is no preceding visual or neurologic aura, but only headache, nausea and vomiting, or even headache alone. Conversely, patients who describe only "sick headaches" throughout their lives are frequently found to have a close relative who has always experienced the "classic" type. Other patients, who describe their first headaches as being of the "classic" variety, in subsequent years suffer only "sick headaches." The close interlocking of these two types of headache, sometimes in the same person and at other times in the same family, makes it seem reasonable to include both types under the general heading of migraine. The type of headache that is preceded by the characteristic neurologic aura has commonly been called "classic migraine," whereas the other type, which has no such dramatic preheadache disturbance, has commonly been termed "atypical migraine," in spite of the fact that it occurs probably ten times as often as the classic variety. Perhaps a better term than "atypical" would be "ordinary" migraine, or "sick headache."

The headache in migraine is steady, and at times throbbing, and is described as pain rather than tightness, pressure, "a band around the head" or in other vague terms commonly used by the patient suffering from tension headaches. The pain is made worse by bending over, moving the head suddenly, coughing and straining or any maneuver that increases the distension of cranial blood vessels. The pain is related in its distribution to the anatomy of the cranial blood vessels, especially the branches of the external carotid artery, rather than to the distribution of any one sensory nerve. Favorite sites are the areas of pain reference of the temporal, middle meningeal, supraorbital and occipital arteries; in some cases pain is experienced in the region of the carotid and vertebral arteries, with radiation into the neck, shoulder and arm. It is frequently unilateral, but not necessarily so. At times it may migrate from one part of the head to another during an attack. In some patients the pain affects alternate sides from one attack to another, whereas in an occasional patient it always occurs in the same location. The pain of migraine is unusual in that it influences the patient to avoid confusion, people, noise, light and strong odors. In addition to nausea and vomiting many disturbances of bodily physiology (mostly those under control of the autonomic system) may occur during the headache, such as pallor, flushing, sweating, chills, slow pulse, frequency of urination, diarrhea, weakness, lassitude and general prostration. A residual hyperesthesia of the scalp in the region affected by the pain is a fre-

quent sequel to a migraine attack. The pain may last only a few minutes in mild attacks, or may go on for several days in severe attacks; occasionally, the frequency of individual attacks may become so great that the patient is suffering continuous headache and may be said to be in "migraine status."

In a considerable number of cases a history may be obtained of the occurrence of travel sickness, cyclic vomiting attacks, "acidosis" attacks and periodic abdominal pain in the early years. In a few patients, after the typical migraine syndrome has become well established, episodes of vertigo, paroxysmal tachycardia, precordial pain or abdominal pain seem to replace temporarily, in a periodically recurring fashion, the usual attacks of migraine. These disturbances are so common in migraine sufferers that many authors consider them "migraine equivalents."[3,4]

Natural History

Several points regarding the natural history of migraine need to be borne in mind when one is establishing the diagnosis. First among these is a positive family history.[5,6] Evidence for inheritance of the migraine trait is so strong that the lack of a family history of migraine should give one considerable cause for hesitation in making the diagnosis. In about 20 per cent of the cases that in other respects meet the diagnostic criteria such a history is lacking or unavailable. In female patients relief during pregnancy is such a constant phenomenon (about 80 per cent)[7] that it is of some use diagnostically. This is especially true of "atypical" or "ordinary" migraine or "sick headaches" and less apt to be so in the "classic" type. The tendency for migraine to be aggravated during periods of stress and increased responsibility and to be relieved under conditions of enforced or "legalized" rest and freedom from responsibility, such as during illness and after operations, is of some diagnostic significance. A history of the occurrence of "migraine equivalents" may be helpful. The tendency for migraine to start during sleep or on awaking, to pick out Saturdays, Sundays, holidays and the first few days of vacation and in general to occur as an aftermath of a period of fatigue, tension or stress may be of diagnostic aid.

Considerable attention has been given in recent years to the personal attributes of those who suffer from migraine, and such considerations may help to establish the diagnosis. Authors who have dwelt on this aspect of the subject[6,8] point out that those who suffer severely from migraine usually tend to be of a slender build, with quick, alert, intelligent responses to questions and situations. The personality is described as characterized by a keen sense of responsibility, a desire to please, overconscientiousness, a striving for perfection in all they do and a preference for suppression of hostility rather than precipitation of "scenes."[9,10] Such characteristics are by no means limited to migraine patients, nor do all migraine patients have them. Nevertheless, they are common enough to be considered corroborative evidence for the diagnosis when they are present.

Manifestations of Abnormal Physiology during Attacks

Since it has been shown that the pain of the migraine attack[11] is usually associated with abnormal distention of the cranial arteries, especially the branches of the external carotid artery, any evidence of cranial vasodilatation during attacks may be useful in establishing the diagnosis. Such information may be derived from direct observation of the patient or from his testimony regarding obvious prominence of superficial vessels, such as the temporal artery, during attacks. Similarly, relief of headache effected by manual compression of superficial branches of the external carotid artery or relief obtained by use of drugs that serve to bring about constriction of these vessels gives evidence that the headache has a vascular mechanism similar to that seen in migraine. In this connection the vasoconstrictive effect of ergotamine tartrate (discussed in the second section of this report) is of especial significance. The specific ability of this drug, when given parenterally early in the attack, to stop the pain of migraine makes it a useful diagnostic as well as therapeutic tool. By and large, headaches that are dramatically stopped by ergotamine tartrate may be said to have a vascular mechanism similar to that seen in migraine and in this sense to be related to migraine, even if clinical features of the syndrome distinguish it from "classic" migraine. On the other hand tests that are designed to evoke cranial vasodilatation and thus to precipitate migraine attacks have much less specific diagnostic reliability and are at times accompanied by unpleasant and even dangerous symptoms. Nitroglycerin, amyl nitrite and histamine[12-14] have been used for this purpose. Similarly, skin tests of sensitivity to histamine and acetylcholine[15] do not seem to be reliable indicators of either the diagnosis or the success of treatment with "desensitizing" doses of these agents.

Exclusion of Organic Disease with Similar Symptoms

The scope of this report does not provide for a complete discussion of the differential diagnosis of migraine, but it does seem worth while to stress certain signs and symptoms that point to serious organic disease that may masquerade as migraine. Whereas every patient with headache deserves a thorough history, physical and neurologic examination, as well as routine blood study and urinalysis, the occurrence of the following phenomena should alert the examiner to the possibility of the presence of organic disease and prompt more extensive laboratory studies, such as x-ray examinations of the skull and cervical region, lumbar puncture, electroencephalogram and even, in certain cases, complete neurosurgical investigation:

A history of injury closely related to the onset of headache. Cervical lesions as well as intracranial disorders should be considered in this situation.

The presence of fever, signs of inflammation or laboratory evidence of an inflammatory process.

The occurrence of unconsciousness or epileptiform seizures during an attack.

The appearance of neurologic signs or symptoms *after* the onset of headache rather than *before* it and persistence of such phenomena after the attack of headache is over. (Berry aneurysms, arteriovenous aneurysms and hemangiomas may behave in this fashion.)

Sudden onset of increasingly severe and frequent headaches in middle or late life.

Frequent and increasingly severe attacks of headache in a young child.

Recurrence of the headache in exactly the same location in each attack.

Failure of a severe headache to respond to the therapeutic measures that have always been effective in the past.

Recurrence of severe headache several times in one day or night, with complete freedom in the intervals. (This may happen in "Horton's syndrome" without representing an organic lesion, but is unusual for migraine and can occur in organic intracranial disease.)

Appearance of headaches "out of the blue" to a person lacking a family history of headache, and failure of the headaches to bear any relation to the causes that usually precipitate migraine.

Migraine may still prove to be the diagnosis in each of the situations listed above, but the presence of any one of them should arouse suspicion in the patient's physician of more serious trouble, make him more guarded in his diagnosis and more watchful of the patient's progress and prompt him, in some cases, to obtain expert neurologic consultation and more extensive laboratory examinations.

It becomes apparent from the foregoing discussion that migraine represents one group, including several members, in the society of episodic human disorders. Certain members of the migraine group have such distinct characteristics that their position is clear-cut beyond question. Others, lacking certain cardinal features, nevertheless possess enough similarity, in either their clinical or their physiologic behavior, to be included in the general group of migrainous disorders. From this concept the following classification emerges:

Definitely "migraine": "classic" migraine; "atypical" or "ordinary" migraine and "sick headache." These entities fulfill most of the criteria demanded by the clinical picture, the natural history and the known pathologic physiology of migraine.

Migraine equivalents: travel sickness, cyclic vomiting, "acidosis" attacks and recurrent bouts of otherwise unexplained abdominal pain, vertigo, paroxysmal cardiac arrhythmias, precordial pain and, very rarely, fever. These entities occur with such frequency as substitutes for the migraine attack in certain persons, or as episodic disorders occurring early in the life of patients who subsequently develop migraine, that they may be considered closely related.

Migrainoid disorders: atypical facial neuralgia, Horton's syndrome ("histaminic cephalgia"), certain headaches occurring in hypertensive patients and certain headaches that present primarily the features of the "tension headache" but nevertheless have a vascular element that responds to ergotamine tartrate. These entities for the most part lack the clinical picture of migraine and fail to follow its natural history, but exhibit features in their pathologic physiology that are similar to that of migraine and thus may claim a certain degree of kinship.

Therapy subsequently discussed in this report will be concerned only with the entities listed above under the heading *Definitely migraine*.

Concept of the Dynamics of Migraine

To approach the treatment of migraine in a rational way it is helpful to have a concept of the mechanisms involved in its production. The medical literature for the past hundred years and more has been full of theories on this topic. These have involved such divergent suggestions for the etiologic factors as autonomic "storms," epileptiform discharges, swelling of the pituitary gland, hormonal imbalance, electrolyte imbalance, allergic reactions, errors of metabolism, psychogenic disturbances, vitamin deficiencies, errors in diet, liver disease, gastrointestinal disorders, cervical and head injury, cervical arthritis and postural deficiencies, and ocular malfunction. Each of these has had its day, and in some cases has led to forms of therapy that have been helpful. Obviously, none of them offer a complete solution to the problem. Certain features of the disease, however, repeatedly emerge and seem to stand the test of time. They are as follows:

There is a strong factor of inheritance.

The cranial vasculature is intimately involved.

Preheadache phenomena are probably associated with vasoconstriction.

The pain of the headache is associated with cranial vasodilatation.

Migraine occurs in response to changes either within the body or in its environment requiring adaptation by the body. Exposure to stress of various sorts, of internal or external origin, brings more migraine; removal from stress or protection against it (? pregnancy) relieves migraine.

Patients with migraine, who suffer from it most, seem to be endowed with a personality that seeks and creates stress and a physiology that handles it poorly.

From these general considerations, with which most students of migraine would agree, a general formulation of the dynamics of the disease can be constructed. It is rough in its outline and many lacunae need filling, but it can serve as a framework to support a rational approach to treatment. The concept is that the migraine patient has inherited a neurophysiologic system (affecting especially the behavior of cranial vessels but also more widespread in its action) that for reasons as yet unknown is peculiarly susceptible to the deleterious effects of a variety of stresses; in many cases the patient is also endowed with a personality that in itself promotes the occurrence of stress. Since the inheritance of the migrainous tendency is a "fait accompli," therapeutic efforts must be directed toward correction of the abnormal behavior of the cranial vessels during the acute attack; fortifying the sensitive vascular mechanism against future onslaughts; bolstering the total bodily economy so that it can better withstand strain; and teaching the patient new attitudes that will make it unnecessary to create stresses and easier to withstand those that everyone must endure.

(To be continued)

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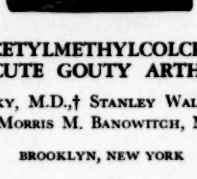
MEDICAL INTELLIGENCE



DESACETYLMETHYLCOLCHICINE IN ACUTE GOUTY ARTHRITIS*

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BROOKLYN, NEW YORK

COLCHICINE has been the drug of choice for the treatment of patients with attacks of acute gouty arthritis because it usually causes prompt and effective symptomatic relief.[1,2] Despite its dramatic, favorable effect in ameliorating the symptoms of this acute arthritis, it may cause gastrointestinal disturbances such as nausea, vomiting and diarrhea, or a combination of these symptoms, which are so severe in some patients as to prevent its use.

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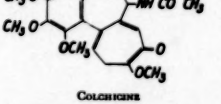
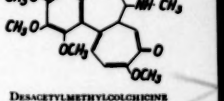
Recent investigations with derivatives of colchicine have shown that although these compounds may retain potent antimitotic activity they produce less systemic toxicity in normal and tumor-bearing mice.[3-6] A natural alkaloid, differing chemically from colchicine in that a methyl group replaces an acetyl group at the N position, has recently been isolated from the plant *Colchicum autumnale*.[7] The respective formulas are as follows:



COLCHICINE



DESACETYLMETHYLCOLCHICINE

The effects of this compound, desacetylmethylcolchicine¶ have been studied in the cat, mouse, rat and rabbit; it is a twentieth to a thirtieth less potent than colchicine in producing general systemic toxicity.[7-11]

In doses not causing systemic toxicity the new compound exhibits antimitotic activity, as evidenced by suppression of granulocytosis in these animals as well as inhibition of growth of some transplantable malignant tumors in the mouse and rat.

Because of the active granulocytic inhibition in the laboratory animals, the drug has been used in the treatment of patients with chronic granulocytic leukemia.[10-12] In some of these patients remissions of the disease have resulted. Little or no tumor-inhibiting

¶Kindly supplied as Colcemide by Ciba Pharmaceutical Company, Summit, New Jersey.

effect has been observed in patients with other neoplastic diseases treated.

The dose has ranged from 1 mg. to 20 mg. daily by mouth. Almost none of the gastrointestinal disturbances commonly observed after colchicine ingestion have appeared.[10-12]

It occurred to us that since desacetylmethylcolchicine so closely resembles colchicine in chemical structure and since it is so much less toxic in both the laboratory animal and the human patient, it might be effective in the treatment of acute gouty arthritis and yet not cause the undesirable gastrointestinal disturbances noted after therapy with colchicine.

Selection of Patients and Dosage

Observations on 10 patients with an established diagnosis of acute gouty arthritis are reported. Eight of these patients had previously been treated with colchicine, with favorable symptomatic response, but gastrointestinal disturbances due to treatment had developed in 4 of the 8 (Table 1).

A total dose of 5 to 8 mg. of desacetylmethylcolchicine in a single course of treatment was administered to each patient because this approximated the dose of colchicine necessary for treatment of an acute attack of gouty arthritis.

Most patients received 1 mg. every hour for five to eight hours. Three patients received an initial dose of 5 mg. and then 1 mg. every hour for three doses. The response to treatment appeared to be similar in both groups.

Results

Nine of the 10 patients who had symptoms of acute gouty arthritis with severe pain in one or more joints responded rapidly with relief of pain and redness when treated with desacetylmethylcolchicine by mouth. Improvement was noted in eight to twenty-four hours after initiation of treatment. Swelling of the involved joints subsided more slowly.

Table 1. *Effect of Desacetylmethylcolchicine in Arthritis.*

Case No.	Uric Acid		Dose	Response	Toxicity	White-Cell Count		Previous Treatment with Colchicine by Mouth	Response	Side Reaction
	Before Treatment	1-4 days after Treatment				Before Treatment	After Treatment			
	mg./100 cc.	mg./100 cc.	mg.							
1	8.5	—	7	Complete relief	None	5900	5100	Yes	Complete relief	Diarrhea
2	5.5	—	8	Complete relief	Mild nausea	—	9900	Yes	Complete relief	Vomiting & diarrhea
3	5.0	4.8	8	Complete relief	None	8300	8200	Yes	Good relief	None
4	9.8	8.8	8	Excellent relief	None	8300	7500	Yes	Fair relief	None
5	6.8	7.0	5	Good relief	None	9150	9050	Yes	None	None
6	5.9	4.4	8	Excellent relief	None	12,600	9100	No		
7	8.1	10.3	8	Good transient relief	Rash(?)	8150	9100	Yes	Fair	Nausea, vomiting & diarrhea
8			5	No relief	None			No		
9	9.5	9.5	8*	Good	None	7500	6500	Yes	Fair	None
			8 (relapse)†	Excellent	None					
10	7.8		8	Excellent	None			Yes	Good	Nausea, vomiting & diarrhea

*On 7/11/54.
†On 7/16/54.

The patient who obtained no relief at all after a total dose of 5 mg. was subsequently treated with colchicine until the appearance of disturbing nausea and diarrhea, and even then there was only partial relief of symptoms.

One patient showed good symptomatic relief after a first course of desacetylmethylcolchicine but relapsed in several days. A second course again produced excellent relief.

Blood uric acid levels were determined in 9 patients before therapy and when repeated in 6 of these patients, one to three days after administration of the drug, showed no significant change in values.

Although the dose administered to these patients was equal to or larger than the average dose of colchicine used in treatment of the acute attack of gouty arthritis, no gastrointestinal disturbances appeared except possibly in 1 patient. Patients who

had previously experienced either nausea, vomiting or diarrhea when taking colchicine, had a total lack of such symptoms after administration of the newer compound.

Undesirable Reactions

In 1 patient a maculopapular rash appeared but subsided rapidly after cessation of drug administration. In another patient mild anorexia of short duration was noted after 7 mg. Granulopenia did not occur in this group. However, because such a possibility exists, this drug should be administered cautiously to patients with gout until more experience has been gathered.

Discussion

Of the numerous agents available for the treatment of acute gouty arthritis none are completely satisfactory. Phenylbutazone may induce prompt effective relief, but complications of therapy such as agranulocytosis, nausea, dermatitis, activation of duodenal ulcer and salt and water retention may occur.[1,2,13-15] Similarly, ACTH or cortisone may also induce rapid improvement in an attack of acute gouty arthritis, but cessation of therapy may result in a severe exacerbation of symptoms.[1,2,16]

Colchicine is probably the most efficacious drug for treatment of the acute attack of gouty arthritis and usually causes rapid, dramatic improvement. Its action is so specific that response of an acute arthritic process is considered diagnostic of gout. Unfortunately, the severe gastrointestinal disturbances caused by colchicine in some patients may prevent its effective use. Desacetylmethylcolchicine appears to be as effective as colchicine in the treatment of acute gouty arthritis but has the distinct advantage of not producing the undesirable gastrointestinal effects often caused by colchicine. It thus appears from the available data that the new compound may be the drug of choice in the treatment of the acute arthritis of gout.

The dose in the group of patients described above was chosen empirically. Much smaller doses may be as effective.

Although we did not encounter any major undesirable effects, a much greater experience is needed before one can be sure that none will occur.

Summary and Conclusions

Desacetylmethylcolchicine, an alkaloid chemically similar in structure to colchicine, was used in the treatment of 10 patients with acute gouty arthritis. Striking relief of symptoms occurred without the gastrointestinal disturbances commonly seen after colchicine ingestion. It appears that the new compound is preferable to colchicine in the treatment of acute gouty arthritis.

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BY THE LONDON POST

Doctors and Administrators — Hospital Planning — Air Ambulance

John Lister, M.D.

London, England

ONE of the results of the National Health Service has been the growth of an enormous army of hospital administrators. Whereas before the service the smaller voluntary hospitals were administered by a house governor, a clerk and a lay committee, most of these hospitals have now multiplied their previous staff many times. Form filling, paying salaries to previous honorary staff members, attending previously nonexistent committees and rendering reports to higher authority are some of the reasons for the increase.

It is the question of higher authority with its centralized control that has probably caused the greatest criticism. In the teaching hospitals a fair degree of autonomy has been retained because they are administered by teaching-hospital boards on which there is usually adequate local medical representation. In the nonteaching hospitals, however, all major decisions of policy are taken by a remote regional hospital board with a local committee of management carrying only limited power.

Before the Health Service the relation between lay administrators and the medical personnel in the hos-

pitals was tolerably good, but the increased authority that the Health Service has inevitably given to the administrators has led to increasing friction. A recent incident provoked a prolonged correspondence in the *Times* and editorial comments both in the lay and in the medical press. A registrar (resident) working in a nonteaching hospital wished to attend a conference. His chief was agreeable to his going and was satisfied with the arrangements made for the care of the patients. Official sanction was sought from the Regional Board, and leave was refused. In spite of this refusal, the registrar attended the conference and was summarily dismissed by the Board for absenting himself without leave. To the lay administrator this doubtless seems the logical outcome of the incident. To many physicians it is regarded, at its best, as an unfortunate example of the abuse of authority. In particular the danger of central control has been emphasized. One correspondent to the *Times* has compared the relation between a registrar and his chief to that between a junior officer and his commanding officer. In normal times, when the former applies for a short period of leave, the latter has the authority to grant it at his own discretion. This reflects the confidence with which the higher authority regards its senior officers and promotes an atmosphere of respect and loyalty between officers at local levels. Such relations are certainly required for the smooth running of hospital units. On the other hand abuse of privilege calls for correction, and it must be admitted in this respect that doctors are often highly individualistic and resentful of discipline.

Dr. Rowland Hill, chairman of the Central Consultants and Specialists Committee of the British Medical Association, has agreed that there must be means of correcting the ways of erring members of hospital medical staffs. He believes, however, that cases of misconduct such as an apparently indefensible absence from duty are often due to misunderstanding and may be as much a reflection on the efficiency of the administrator and his relations with the staff as on the member of the staff concerned. He therefore urges a full inquiry into hospital administration with a view to establishing machinery that will allow the fullest consultations between the administrative authority at all levels and representatives of the medical staffs of hospitals.

To the cynic these notes may reflect just another stage in the transformation of the medical fraternity from a profession to a service. To the idealist it should be a challenge to doctors and administrators to work together to create an atmosphere in which the best possible treatment can be obtained for the patients.

* * *

All those engaged in planning new hospitals will welcome the report of an investigation into the function and design of hospitals carried out by a team sponsored by the Nuffield Provincial Hospitals Trust and the University of Bristol. Under the direction of an architect, the team included a statistician, historian, physician, nurse, accountant and several field research assistants. Because it had already been found that on many key problems, opinion was often sharply divided, the team arrived at the collection of objective data rather than of opinion. Their studies fell into three principal groups: the study of individual hospital departments; the study in physical environment concerning such questions as lighting, heating, ventilation, color and the control of noise; and the study of the actual demand or case load that may be made on the hospital services of an area. Studies of individual departments covered the wards, the outpatient services and the operating rooms. The study of the case load involved a pilot survey of the demand for hospital facilities from a population of approximately 400,000 and a detailed study of the demand from a population of 500,000. The research has covered a wide field, ranging from the main disposition of hospital buildings to an analysis of a nurses' route around the ward in a single tour of duty and from color schemes and outpatient appointment systems to the right number of beds in a ward.

The report of the team's findings is highly technical, and yet it makes fascinating reading. It is important in several ways. In the first place, it provides factual and scientific information without which the National Health Service cannot properly develop; secondly, it is a rare example of an investigation carried out by a team drawn from several professions; thirdly, the team was fortunate in being invited to plan and build a medical unit in Scotland and a surgical unit in Ireland. By this means, it was able to interpret its findings in terms of bricks and mortar and patients and thus to check and revise its work in the light of genuine experiment.

In summarizing the results of its work the team has stressed the importance of planning all hospital facilities to meet the demand of the community they are to serve. Although this is a simple principle it is only since the introduction of the National Health Service that any effective co-ordination in this respect has been possible. The case-load surveys carried out by the team showed that the hospital groups studied were meeting the demands for acute beds satisfactorily but that the chief requirement was the reallocation of beds between specialties. The team believes that more case-load surveys are needed and that for direct planning purposes, whether in modifying existing hospital facilities or in establishing new ones, an *ad hoc* survey should usually be undertaken to determine the exact demands of the community concerned.

* * *

It is rare to hear a doctor enthuse about the National Health Service. It was refreshing, therefore, even though the circumstances were most unfortunate, to read a letter from a colleague the other day. He explained how he had been on holiday in

the Hebrides walking on the moors with his wife, who had slipped into a peat bog and dislocated her ankle. After some delay, an ambulance arrived not far from the scene, and the patient was transported to the air strip on the island, where a four-engined Heron Ambulance aircraft was awaiting.

The patient was immediately flown to a hospital in Glasgow, where x-ray examinations were carried out and the diagnosis confirmed. Since the doctor lived near London the patient was flown the same day to London Airport, where an ambulance met the aircraft and drove the patient to a London nursing home. From there on her treatment would be private, but up to that point it had been on the National Health Service. The doctor's only comment was, "What a service. Can you beat it?"

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41431

PRESENTATION OF CASE

A nineteen-year-old single girl was admitted to the hospital because of crampy pain in the lower abdomen.

The patient was in good health until four months previously, when she experienced the onset of pain in the right lower quadrant of the abdomen, nausea and vomiting. After she had been in bed for two days the symptoms subsided except for soreness in the right lower quadrant, intermittent chilly sensations and malaise, which persisted for about ten days. Intermittent twinges of pain in the lower abdomen continued thereafter. One day before admission she again became nauseated, vomited continually and suffered crampy bilateral suprapubic pains. The vomitus was liquid, clear yellow and bitter. There were alternate feelings of chilliness and warmth. Although she had passed gas by rectum the day before and the day of admission, she did not pass stools on these days. She recently noticed slight urinary frequency. However, there was no burning, pain, hematuria or pyuria. As well as she could recall, the menstrual periods, which occurred regularly once a month, were always normal, including the previous one and the current one, which had started two days before admission. There was no history of intermenstrual bleeding or discharge. The patient disclosed that she last engaged in sexual intercourse one month before admission, but that prophylactic measures against conception had been taken. She denied any previous pregnancies or attempts at abortion.

The past history and systems review were noncontributory except for a weight loss of 3 or 4 pounds over the previous four months.

Physical examination revealed a well developed and well nourished female in whom significant findings were limited to the abdomen and pelvis. A soft, round mass was felt rising out of the pelvis to a point just below the umbilicus. There was no guarding of the abdominal muscles, and the liver, spleen and kidneys could not be felt. Peristalsis was slightly hypoactive. Pelvic examination revealed a marital introitus and a soft bluish cervix, with dark blood exuding from the external os. The large mass felt on abdominal examination appeared to be about the size of a four-month or five-month fetus; a mass 4 cm. in diameter was palpable in the right adnexa, protruding into the right vaginal fornix. In the cul-de-sac was an exquisitely tender mass pushing toward the rectum.

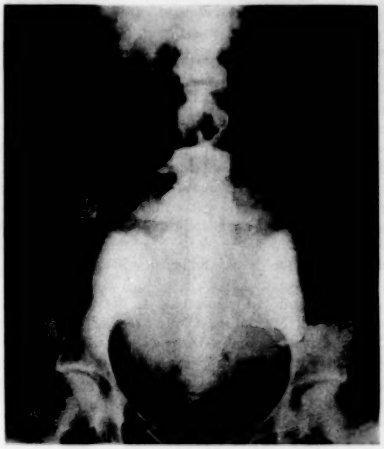

FIGURE 1. *Roentgenogram of the Pelvis.*
A large, smooth, homogeneously dense, ovoid mass arises from the pelvis and extends into the lower abdomen (arrows).

The temperature was 98°F., the pulse 80 and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.4 gm. per 100 cc., a white-cell count of 15,400 and a prothrombin time of 100 per cent. The serum amylase was 10 Russell units per 100 cc. X-ray examination of the abdomen showed a mass the size of a five-month pregnancy rising from the pelvis to the level of the body of the fourth lumbar vertebra (Fig. 1). No fetal parts or calcifications were seen. No free air was seen in the peritoneal cavity.

Six hours after admission an operation was performed.

Differential Diagnosis

Dr. Francis M. Ingersoll*: I should like to examine the x-ray films to see if they will give me additional help.

Dr. C. C. Wang: The film of the abdomen reveals a large soft-tissue mass in the lower abdomen that is fairly smooth in outline and measures approximately 12 cm. in diameter (Fig. 1). Within this mass no unusual calcification or fetal structure can be recognized. Moderate amounts of gas and feces are scattered in the colon. A film of the abdomen with the patient upright gives no evidence of free air to suggest a perforation of a hollow viscus.

Dr. Ingersoll: Was the amount of gas in the small bowel interpreted as too much? Would that indicate small-bowel obstruction?

Dr. Wang: The amount of gas in the small bowel is somewhat more than usual, but there is no localized dilatation of the bowel.

A Physician: Had the bladder been emptied before the x-ray films were taken?

Dr. Ingersoll: I should assume that it had. The practice in the Emergency Ward is to empty the bladder during the catheterization — not just to take a specimen.

The patient's symptoms largely pertained to the gastrointestinal tract, with the exception of the pain, which could be attributed to any viscus within the abdomen. The acute episode started on the second day of the menstrual period, just one day before admission, and an operation was done only six hours after admission. The rapidity with which the operation was done is, I think, significant. The physical examination showed three masses: the very large mass, which was seen in the x-ray film and which I should believe was not a normal pregnancy because at that size due to pregnancy it should have contained some fetal parts visible in the x-ray films; a mass in the cul-de-sac, which was exquisitely tender, and whose size was not stated; and a smaller mass in the right adnexal region. The blue cervix may be significant, or it may be a "red herring." The laboratory data revealed that the patient was suffering from either infection or infarction. The fact that the temperature was normal does not help. I should say that a person in my position can only express his belief that a description of the pelvic examination does not give him the clear idea of the condition present that his doing the examination would.

The first and easiest task is to eliminate certain pathologic conditions of the gastrointestinal tract. Pancreatitis was considered by the physician who saw her, but the amylase was normal. Certainly, it would be difficult to consider that. In this age group, conditions like ulcerative colitis, perforated bowel and diverticulitis I consider highly unlikely. I shall discuss later the problem of appendicitis.

I must consider pregnancy and its complications because the patient was at a susceptible age and had been exposed to the possibility. The history was not consistent with that diagnosis. She had no abnormal bleeding or amenorrhea. The periods were regular, and the last normal one had just started. Moreover, the symptoms were mainly related to the gastrointestinal tract. On the other hand, it is perfectly possible to account for the findings on physical examination by an abnormal pregnancy. The x-ray findings are against a normal intrauterine pregnancy. Among the types of pregnancies to be mentioned is ectopic pregnancy, which I think I can rule out; I have never seen an ectopic pregnancy with a mass of this sort. I have to consider a normal pregnancy, complicated by a twisted cyst behind the uterus. Having seen the x-ray films, I think I have to eliminate that possibility. The thought went through my mind that this was an abdominal pregnancy — that about four months previously the tube had ruptured and extruded the pregnancy, which grew in the abdomen. Again, the x-ray film would probably have enabled me to make that diagnosis. I consider it unlikely that the patient was pregnant and suffered any complication of pregnancy.

A more likely possibility is a gynecologic condition such as a twisted ovarian cyst. The pain four months previously, unless the cyst had twisted at that time also, is difficult to reconcile with this diagnosis. Moreover, the malaise and weight loss could hardly be explained on the basis of a twisted viscus. The acute episode with which she was admitted and the pelvic mass seen on the film then could be interpreted as the result of this condition. The adnexal mass could have been the other ovary. The physical examination supports this diagnosis; the history is against it.

I shall now proceed to the discussion of two other possibilities, appendicitis and pelvic inflammatory disease, which must be considered in the differential diagnosis. An inflammatory condition best fits the facts presented in this case. Pelvic inflammatory disease and appendicitis could account for the episode four months before admission. I do not think one

*Assistant surgeon, Massachusetts General Hospital.

could differentiate between the two conditions at the onset from the history given here. The facts that she had pain for ten days after the first attack and that she had continued abdominal pain during these four months certainly strongly suggest that some episode of inflammatory nature happened four months before admission. The strong objection to appendicitis is the physical examination since three masses were described, the large nontender abdominal mass and two pelvic masses. An appendiceal mass of this size would present a physical examination quite different from the one here. The same is less true of pelvic inflammatory disease, although a chronically dilated tube is more likely to present as a smooth mass without spasm and tenderness than appendicitis is. It is difficult to reconcile the physical findings with a diagnosis of inflammatory disease — either appendicitis or pelvic inflammatory disease — because with inflammatory disease that had produced this large a mass, the examiners would not be able to delineate pelvic masses in the other two places. The organs in the pelvis would be indurated, and discrete masses such as are described here are not usually felt.

I have considered the various possibilities and have found no one diagnosis that to me explains all the features of the history and x-ray and physical examinations. The three likely diagnoses are acute appendicitis, with subsequent abscess formation, a twisted cyst of the ovary and pelvic inflammatory disease, with a large tubo-ovarian abscess. It seems to me that the last diagnosis fits the data the best.

DR. BENJAMIN CASTLEMAN: Would anyone like to question Dr. Ingersoll?

DR. REED HARWOOD: This mass must have been readily palpated by the patient. Was there any note in the history to indicate that she was aware of its being there?

DR. CASTLEMAN: Apparently not. Do you know about that, Dr. Dunn?

DR. EDWARD DUNN: I do not believe that she was aware of the mass.

DR. JACOB LERMAN: I should like to ask Dr. Ingersoll if it is not true that patients who have large ovarian cysts have episodes of pain as the result of partial twisting and untwisting of the cyst.

DR. INGERSOLL: That is true and is one of the reasons why I considered it strongly. However, the ten-day history with the first attack, the loss of weight and the gastrointestinal symptoms over four months seemed to argue against a twisted cyst.

A PHYSICIAN: Was there any evidence of shock on admission?

DR. DUNN: No; she was not in shock.

DR. INGERSOLL: Did any observer state the size of the mass in the cul-de-sac? It would have been helpful to have a more precise description of that separate mass.

DR. DUNN: I do not recall the size of the mass.

DR. ALLEN G. BRAILEY: Could she have had a hydatiform mole?

DR. INGERSOLL: I think that is one of the possibilities. Four months previously there may have been a miscarriage with the development of a mole. I have too much trust in the surgeons to believe that they operated on a patient for a hydatiform mole after only six hours' observation.

A PHYSICIAN: I should like to suggest a partially twisted ovarian cyst rather than a tubo-ovarian abscess.

A PHYSICIAN: Could it have been a carcinoma of the ovary?

DR. INGERSOLL: If it was a cyst, I do not think anyone can say whether it was malignant or not.

A PHYSICIAN: How often does a soft-tissue mass other than a dermoid show so clearly in the x-ray films?

DR. WANG: Very often, especially when the border of the mass is outlined by gas in the bowel.

DR. ELBERT P. TUTTLE, JR.: How could you explain the symptoms suggestive of intestinal obstruction?

DR. INGERSOLL: I thought the obstruction of the bowel was secondary. That was one of the main reasons why I chose an inflammatory process. The history of continual vomiting is difficult to reconcile with a twisted cyst, although the pain with a twisted cyst could give symptoms of intestinal obstruction.

A PHYSICIAN: How did you explain the blood noted exuding from the external os on physical examination?

DR. INGERSOLL: I thought it was menstrual. Probably, it accounted for the blue cervix.

DR. CASTLEMAN: Does the pressure from an abdominal mass ever produce a blue cervix?

DR. INGERSOLL: It is not supposed to.

DR. CASTLEMAN: Could it cause enough engorgement of the vessels to do that?

DR. INGERSOLL: A twisted cyst in the cul-de-sac might cause enough venous congestion to cause this.

CLINICAL DIAGNOSIS

Twisted ovarian cyst.

DR. FRANCIS M. INGERSOLL'S DIAGNOSIS

Tubo-ovarian abscess.

ANATOMICAL DIAGNOSIS

Twisted para-ovarian cyst, with infarction and necrosis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Under anesthesia another pelvic examination was carried out. Dr. Grant V. Rodkey stated that he believed that the uterus could be separated posteriorly from the larger mass in the abdomen, which arose from the pelvis to a point about

2.5 cm. above the umbilicus. The second mass, in the right vault, seemed to be attached to the larger mass. His preoperative diagnosis was twisted ovarian cyst; he interpreted the second mass as the pedicle of an ovarian cyst that had twisted. At operation as soon as he opened the abdomen, he encountered a fair amount of serous fluid, which he aspirated. A large irregular black mass occupied the right pelvic area and extended above the umbilicus. He believed that this was an ovarian cyst and that the second mass was the pedicle. He put a clamp across the pedicle, but could not remove the cyst because it was so large. Therefore, he reduced the size of the mass by aspirating the fluid in it until it was small enough to remove intact.

The specimen we received was a hemorrhagic infarcted mass across the top of which was the fallopian tube and at one end of which was a small ovary that seemed to be separate from the mass. The infarcted mass, therefore, was a para-ovarian cyst that had twisted and infarcted not only itself but the small normal-sized ovary nearby. The left ovary and tube were normal. Para-ovarian cysts are often of this size, have very thin walls and contain clear fluid. Parts of the infarcted mass appeared older than others, and it is very likely that the attack four months previously was the result of a partial twist.

CASE 41432

Presentation of Case

A seventy-three-year-old woman was admitted to the hospital because of jaundice.

Two and a half weeks previously the skin and scleras were noted to be icteric. Her family physician found bile in the urine and clay-colored stools. She was placed on a fat-free diet and given some pills. The icterus diminished somewhat, and the urine became lighter and the stools darker. There was no history of fever, chills, abdominal pain, fatty-food intolerance, change in bowel habits or bloody or tarry stools. There was no exposure to jaundiced persons or to hepatotoxins. She had received no injections. Her appetite had been good until three days before admission. Dietary intake was adequate. She consumed one glass of wine each day with her dinner. There had been no previous episodes of jaundice or significant loss of weight.

The patient had hypertension for five years. Three years before admission she had been hospitalized elsewhere for a stroke, which resulted in a left-sided hemiparesis. Since then she had been maintained on hypotensive drugs (lately Serpasil) and on a low-sodium diet. She had orthopnea relieved by two pillows, but no paroxysmal nocturnal dyspnea.

Physical examination revealed a deeply jaundiced woman, who was somewhat sluggish. The heart was slightly enlarged to the left. A Grade 2 systolic murmur was heard at the apex. There were medium moist rales at both lung bases and on the right side of the chest up to the angle of the scapula. A sharp, smooth liver edge was felt 5 cm. below the right costal margin. The spleen was not palpable. The abdomen was not tender, but a positive Murphy sign was elicited. No spider angiomas were seen.

The temperature was 99°F., the pulse 96, and the respirations 16. The blood pressure was 140 systolic, 60 diastolic.

Figure 1. *Roentgenogram from Gastrointestinal Series, Showing Irregularity along the Proximal-Greater-Curvature Aspect of the Stomach (Arrows).*

Urinalysis showed a specific gravity of 1.021, negative tests for albumin and sugar, a ++++ test for bile and 0.64 Ehrlich units of urobilinogen; the sediment contained 7 to 15 white cells and 5 to 10 red cells per high-power field. Examination of the blood revealed a hemoglobin of 8.4 gm. per 100 cc. and a white-cell count of 13,700, with a normal differential. The serum iron was 40 microgm. per 100 cc. The blood Hinton test was negative. The bilirubin was 21.2 mg., the total protein 7.4 gm., the albumin 3.0 gm., the globulin 4.4 gm., with an albumin-globulin ratio of 0.7, the nonprotein nitrogen 21 mg., the alkaline phosphatase 5.7 units, the fasting blood sugar 93 mg., the cholesterol 85 mg., and the cholesterol esters 64 mg. per 100 cc., and the cholinesterase 0.14 delta pH units per hour. The serum sodium was 133 milliequiv., the potassium 3.4 milliequiv., and the chloride 98 milliequiv. per liter. The prothrombin time was 16 per cent of normal. Cephalin flocculation was ++++ in twenty-four and forty-eight hours. The blood ammonia was 145 microgm. per 100 cc. (normal, 40 to 80 microgm.). A guaiac test on the stool was +. In an electrocardiogram, which was interpreted as showing severe myocardial disease or electrolyte disturbance (including low potassium),

there was a nonsinus rhythm at a rate of 90, a PR interval of 0.20 second, a QRS interval of 0.08 second, a prolonged QT interval, a normal axis, occasional premature ventricular contractions and inverted T waves in Leads 1, aVL, V_2, V_3, V_4, V_5 and V_6. An x-ray film of the chest showed cardiac enlargement and suggestive evidence of pulmonary congestion. An upper gastrointestinal series was reported as probably negative, but a large pressure defect was noted at the junction of the fundus and body of the stomach along the greater curvature (Fig. 1). This might have been enlarged gastric folds or an enlarged spleen.

The patient was placed on a high-caloric, high-vitamin diet and ferrous sulfate by mouth. She was given a unit of packed red cells, and a Penrose tube was inserted into the stomach, since she was taking oral feedings poorly. A second electrocardiogram on the sixth hospital day revealed no significant change since the preceding tracing, with evidence of hypertrophy of the left ventricle and ischemia of the anterior wall. The urinary urobilinogen on the fourth hospital day was 5.1 Ehrlich units, and on the eighth hospital day 0.88 units. Several stool guaiac tests were negative. The patient's condition gradually deteriorated, and she lapsed into coma on the twelfth hospital day. At this time the blood ammonium was 218 microgm. per 100 cc. Protein intake was stopped, and glutamic acid, 15 gm. four times a day, Meticorten, 100 mg. daily, an injection of 2 liters of 25 per cent dextrose in water with 20 milliequiv. of potassium chloride and Aureomycin, 500 mg. daily, were given. Two days after glutamic acid therapy, the serum ammonia fell to 114 microgm. per 100 cc. However, the patient's mental status improved only slightly. The abdomen gradually became distended with gas and fluid. The liver was stated to be no longer palpable on the sixteenth hospital day. Four days later, the patient became hypotensive (blood pressure 85 systolic, 55 diastolic), the heart sounds became weak, and she became dehydrated and oliguric. A systolic gallop appeared in the fourth intercostal space over the right sternal border. The lungs were clear except for a few sparse inspiratory rales at both bases. The neck was stiff, and reflexes were increased on the left side. The serum potassium was 6.4 milliequiv. per liter, and the nonprotein nitrogen 129 mg. per 100 cc. An electrocardiogram showed T-wave changes suggestive of potassium intoxication and some evidence of myocardial ischemia. On the next day the hemoglobin was 12.5 gm. per 100 cc., and the white-cell count 45,000. A urinalysis showed a ++ test for albumin, and the sediment contained a moderate number of white cells, rare red cells and 1 to 2 granular and hyaline casts per high-power field. A finger specimen of stool was silvery black and gave a ++ guaiac test. The patient was now flaccid, with shallow gasping respirations. There was marked edema of the face, hands and legs. The saphenous veins were noted to be thrombosed. She passed 400 cc. of liquid tarry stools and died several hours later on the twenty-first hospital day.

Differential Diagnosis

Dr. Earle M. Chapman*: How many of you know what Murphy's sign is? Seven people. Murphy† described tenderness in the right upper quadrant on deep inspiration that he thought was due to disease in the region of the gall bladder. Actually, it has no special origin; it can be from a tender liver.

Dr. Wang, will you show the films?

Dr. C. C. Wang: Films of the chest show considerable pulmonary congestion and cardiomegaly, chiefly in the left ventricle; the aorta is quite tortuous. There is no fluid at either pleural cavity. A gastrointestinal series demonstrates some irregularity along the proximal portion of the greater curvature (Fig. 1). Unfortunately, the fluoroscopist did not observe this finding so that no spot film of it was obtained. I should interpret this area in the upper greater curvature as suggestive of an organic lesion of the stomach.

Dr. Chapman: Is the moth-eaten border the kind seen with carcinoma of the stomach?

Dr. Wang: Yes; it could represent carcinoma of the stomach. The spleen is not enlarged.

Dr. Chapman: It does not look enlarged on the films, and there was no palpable enlargement of the spleen.

Dr. Wang: No gallstones are seen.

Dr. Chapman: Are there any signs of varices in the esophagus?

Dr. Wang: I cannot see any.

Dr. Chapman: I take it that the patient was not studied carefully for varices.

Dr. Wang: No; she was not.

Dr. Chapman: The problem is, Why did this seventy-three-year-old woman, with jaundice and anorexia, deteriorate steadily in spite of the best efforts of the medical service and die three weeks after admission, with what seems to have been clear evidence of a severely injured liver? The question arises whether the liver was injured directly from intrinsic disease or whether it was damaged as a result of a primary disease that lay at a distance from the liver. Yet all the laboratory evidence does not clearly define this. I might say that she had a mixed type of jaundice, since some features suggest obstructive and some nonobstructive jaundice. But if I pick out certain tests in reconstructing the case, I can make the findings fit together. I am going to consider the positive Murphy sign first and say that I do not believe that this woman had biliary-tract disease per se — cholecystitis or cholelithiasis. If she had carcinoma of the

*Physician, Massachusetts General Hospital.

†Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S. *Diseases of the Gall Bladder and Bile Ducts.* 477 pp. Philadelphia: Lea & Febiger, 1928. P. 174.

head of the pancreas, the gall bladder should have been enlarged and she would have had another positive man's-name sign — Courvoisier's law; but no one palpated the distended gall bladder and the picture does not fit with a totally obstructive jaundice. I am going to rule out a completely obstructive jaundice, perhaps unwisely, on the basis of one test, the normal alkaline phosphatase of 5.7 units per 100 cc.

What was going on in the liver? We know that she was addicted to drinking wine each day for many years, and yet there was not much evidence for cirrhosis. Against cirrhosis would be the facts that there were no varices, that the spleen was not enlarged, that she had been perfectly well until the final illness and that she had no ascites. The story of her illness just does not fit with cirrhosis.

Then, what was disturbing the liver? I suggested, when Dr. Wang was reading these films, that she had a carcinoma of the fundus of the stomach. I do not know whether the Service made that diagnosis, but if I had been given this case and told the x-ray films were normal except for a pressure defect along the greater curvature of the stomach, I should have been inclined to make that diagnosis, particularly since the defect looks like an intrinsic one.

Dr. Wang: It is difficult for me to be certain of that.

Dr. Benjamin Castleman: Apparently, this patient was unco-operative and moved about during the x-ray examination. The radiologists said the gastrointestinal tract was probably normal, but an intrinsic lesion on the greater curvature could not be excluded on the spot films.

Dr. Chapman: The radiologists often have difficulty in identifying carcinoma that lies in the greater curvature of the stomach. The liver edge was sharp and smooth. No one felt nodules in the liver so that I cannot say that it was a hobnail liver with a hepatoma developing within it; there may have been extensive metastases within it. One laboratory test that would fit with carcinoma is the new test for the cholinesterase, which revealed 0.14 delta units. That is an exceedingly low cholinesterase. Am I right, Dr. Point, in saying that the physicians who brought out this test said that such a low result is compatible with diffuse cancer within the liver? I am troubled by the low cholesterol of 85 mg. per 100 cc. There, again, a destructive process in the liver might interfere with the formation of cholesterol, so that too might fall in line with this diagnosis. The cephalin flocculation is a nonspecific test that when ++++ indicates a great deal of liver damage and is consistent with the diagnosis.

Finally, I come to the course of this patient. We know that patients with carcinoma of the stomach, like those with carcinoma of the pancreas, are subject to thromboses of the vessels in the peripheral areas. The final episode within the abdomen may well have been mesenteric thrombosis. The white-cell count went up to 45,000, she went into a state of collapse, and yet the hemoglobin did not fall. The final point is that she had blood in the stool, with a positive guaiac test on admission, followed by several negative tests while she was on tube feedings during which the food perhaps was deposited below the lesion and did not irritate it very much. Terminally, she had massive bleeding into the gastrointestinal tract, either from the lesion itself or perhaps from an infarcted bowel as the result of mesenteric thrombosis.

In reconstruction, then, I think that she did have carcinoma of the stomach, with metastases to the liver. I might add that the red cells in the urine were related to the jaundice and that she did not have intrinsic renal disease.

Dr. Castleman: Dr. Point, have you a comment?

Dr. Warren Point: In the first place I think the cholinesterase test is not specific for metastatic cancer of the liver, and it has been useful more as an index of severe liver dysfunction, which seemed to be confirmed here. I think the objective evidence given in the protocol is more in favor of an overwhelming infectious or toxic hepatitis, and I should raise that as a possibility. If one takes literally the statement that the liver could not be palpated on the sixteenth hospital day and interprets that to mean that the liver had shrunk, it becomes difficult to maintain that there was metastatic cancer of the liver. Of course, at that time, the abdomen was distended with fluid and gas, and I suppose that could be one reason that the liver was not felt. I think it is somewhat awkward to accept a diagnosis of acute hepatitis, either toxic or epidemic, as the cause of a seventy-three-year-old woman's death, particularly since she had no known history of previous or recent exposure to infectious agents. There is a question of carcinoma of the stomach so that it is possible that carcinoma did spread to the liver. On the basis of experience, however, I should lean toward a toxic or infectious hepatitis. Of course, overwhelming metastatic cancer can produce a picture simulating hepatitis or cirrhosis.

Dr. Chapman: I accepted the statement that she had no hepatotoxins, but when the protocol said that she was given "some pills," I wondered if they contained a hepatopoison like Thorazine.

Dr. Castleman: Thorazine can produce signs of obstruction and a lowered phosphatase. Those are against a metastatic cancer.

Dr. Farahe Maloof: Would Dr. Chapman agree that the hemoglobin of 12.5 gm. per 100 cc. was high for a patient who went into shock and had so much blood in the stools? I should question that value.

Would you consider carcinoma of the pancreas, which could produce the defect on the stomach noted in the gastrointestinal series?

Dr. Chapman: I considered carcinoma of the pancreas and discarded it. I thought that the hemoglobin of 12.5 gm. per 100 cc. might have been the

result of hemoconcentration; mesenteric thrombosis with massive hemorrhage would produce a fall in blood volume, but she had only a + guaiac test so she did not have severe hemorrhage.

DR. POINT: I assume that she was transfused when she came in.

DR. RICHARD V. WILSON: That defect in the stomach is somewhat high to be caused by the pancreas; it is usually lower and on the body of the stomach.

CLINICAL DIAGNOSES

Parenchymal liver disease.
Peritonitis.
Pyelonephritis.

DR. EARLE M. CHAPMAN'S DIAGNOSIS

Carcinoma of stomach, with metastases to liver.

ANATOMICAL DIAGNOSIS

Hepatitis, acute, viral or toxic.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At autopsy we found that the stomach was perfectly normal; there was no evidence of carcinoma anywhere. The liver certainly could not have been felt before death because even at death it was 2 or 3 cm. above the costal margin — an extremely small liver weighing only 900 gm. At autopsy we thought this might be acute yellow atrophy or acute hepatitis. There were hemorrhages throughout the body. Those in the bowel accounted for the blood in the stool.

On microscopical examination there were severe degenerative changes in the liver. In most areas the liver cells were completely destroyed. There was quite a bit of inflammation in the portal areas and some in the areas of necrosis. Characteristically, when hepatitis is this severe, a reticulum stain will show the framework of the liver still remaining but compressed as the liver cells fall out. This was true in this case. Whether this hepatitis was of the viral or of the toxic type, I do not know. To me it would fit in quite well with a viral hepatitis of a fulminating nature. The patient lived for four or five weeks after the onset, with which I think the picture in the liver would fit. The occasional liver cells that are left seem to be normal so that if she had lived a little longer they would have regenerated.

DR. MALOOF: Is hepatitis likely to be more severe in this age group?

DR. CASTLEMAN: Yes; in a woman beyond the menopause hepatitis is usually severe.

A PHYSICIAN: How do you explain the gastrointestinal bleeding?

DR. CASTLEMAN: Any patient who has severe hepatitis may have hemorrhages anywhere; in this case they were found in almost all the organs. The hematuria, for example, was due to hemorrhage into the pelves of the kidneys.

DR. MALOOF: What did the kidneys show?

DR. CASTLEMAN: The kidneys contained a fair number of hemocasts in the collecting tubules such as are seen with hepatitis.

A PHYSICIAN: What did the heart show?

DR. CASTLEMAN: The heart was enlarged, weighing 500 gm., and was hypertensive in type.

DR. CHAPMAN: Were vascular thromboses present?

DR. CASTLEMAN: No; and there was no evidence of injury to the myocardium.

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OCTOBER MEETING OF THE COUNCIL

THE Council of the Massachusetts Medical Society, during the course of a stated meeting held at the Boston Medical Library on October 5, approved the plan of the Committee on Finance for the establishment of a charitable and educational fund to be administered by a board of five directors. With the establishment of such a fund gifts or income of a similar nature can be accepted tax free to become a part of it.

The Committee on Hospital and Professional Relations recommended no action in a dispute relative to a disagreement concerning a survey made of the surgical department of the Leominster Hospital. The matter was referred back to the Committee for further study.

One of the most warmly debated reports was that of the Committee on National Legislation relative to the extension of compulsory social security to physicians under Old Age and Survivors Insurance, and, of even greater importance, the proposal that benefits for permanent and total disability be removed from Public Assistance and put under Old Age and Survivors Insurance, where a needs test would no longer be required. This bill was passed by the House late in the last session and will come up for action in the Senate soon after Congress reconvenes.

Dr. Nicholas S. Scarcello, whose communication on the subject appears elsewhere in this issue of the *Journal*, had previously moved in the Executive Committee to recommend to the Council that each district society should discuss this matter and a record of its vote be forwarded to the Secretary of the State Society before December 1. This recommendation, which had been accepted by the Executive Committee, was adopted by the Council.

The report of the Committee on National Legislation is itself a masterly presentation of the development of modern social security from its inception in Great Britain in 1912 to the present An abstract of it was published in the *Journal* of September 8, 1955, and the complete report as accepted by the Council has already been reprinted from the *Circular of Advance Information for Councilors* and mailed to each fellow of the Society in order that he may acquaint himself more fully with the subject prior to the coming debates.

Dr. Frank N. Allan, for the Committee on Pharmaceutical Problems, reported on a resolution passed by the Massachusetts State Pharmaceutical Association "deploring and condemning" the recent revision of the *Principles of Ethics of the American Medical Association* to the effect that "it is not unethical for a physician to prescribe or supply drugs, remedies or appliances as long as there is no exploitation of the patient." This action supplanted a revision of the *Principles of Ethics* made in 1954 to the effect that it was unethical "for a physician to participate in the ownership of a drugstore or to dispense drugs or

appliances unless adequate facilities were otherwise unavailable."

The resolution further urged the Massachusetts Medical Society to indicate its disapproval of the action of the House of Delegates of the American Medical Association, and advanced the startling claim that it is illegal for the physician to dispense drugs to his patients.

This claim of illegality is based on a new interpretation of a clause in the law passed by the Great and General Court of Massachusetts in 1955, to become effective January 1, 1956, which, if the interpretation were accepted, would apparently make it illegal and heavily punishable, by a fine of $1,000, for a physician to give away an aspirin tablet. Such an interpretation would divert the effect of the law from the protection of the patient to the protection of the druggist. This urgent matter was referred by the Council to the Committee on State Legislation for study and action.

Despite nearly five hours of debate, sometimes heated and often tortuous, the meeting ended in a spirit of harmony and mutual regard.

THE FACTS OF MEDICINE

UNDER this title Station WGBH-TV, Channel 2, inaugurated on October 6, 1955, a series of broadcasts sponsored jointly by Harvard Medical School and the Lowell Institute and supported by a grant from the John Hancock Mutual Life Insurance Company. Like all recent undertakings of the educational, noncommercial broadcasting ventures, this is an experiment — one in the field of public-health education. At present it is planned as a series of 40 weekly broadcasts to take place on Thursdays at 8:30 p.m.

The importance that this station and its sponsors attach to this experiment is shown by the fact that the director, Mr. Parker Wheatley, is himself participating in the broadcasts, representing the layman's point of view. His role, as evidenced in the first of these broadcasts, appears to be that of seeing that the material is presented clearly and that it can be understood by the average listener, who, in this instance may be assumed to be at least of average intelligence but not necessarily engaged directly in medical pursuits.

The person immediately responsible for collecting, correlating and interpreting the material for the broadcasts is Dr. David D. Rutstein, professor of preventive medicine at Harvard Medical School. He has undertaken to present the "facts" of medicine as related, whenever possible, to topics of current interest in the news. Opinions expressed are based on available facts, — or the absence and the need for such facts are stressed.

The first broadcast of this series was on the timely subject of the Salk poliomyelitis vaccine and, naturally, was of great interest. Dr. Rutstein stressed and deplored the failure to bring before the scientific world and the medical profession the important facts on which decisions affecting large numbers of people and the entire medical profession were based before, rather than long after, those decisions had been made and acted upon. On this aspect he also quoted directly from an editorial in one of these columns that dealt with this subject.

Judging from this auspicious beginning, the series should prove highly informative and stimulating and also, it is hoped, very popular among physicians, their patients and the general public. The sponsors of this program and the John Hancock Mutual Life Insurance Company, which is supporting it, are to be congratulated for this important undertaking.

GENERAL PRACTITIONER OF THE YEAR

EACH fall since the custom was instituted in 1949 it has been the privilege of the Massachusetts Medical Society to select a General Practitioner of the Year. His name and qualifications are turned over to a special committee of the American Medical Association as the Massachusetts nominee for the Association's General Practitioner of the Year award.

This year, the Executive Committee selected as the Massachusetts nominee seventy-nine-year-old Dr. Henry W. Godfrey, of Auburndale, whose name was submitted by the fellows of the Charles River District Medical Society.

Designed originally as a promotion to focus attention on the general practitioner and his contribution to American medicine, the annual selection of a General Practitioner of the Year has become somewhat of a tradition, looked forward to at each clinical session of the American Medical Association. This year's clinical session will be held in Boston, November 28 to December 2. The name of the physician chosen will be announced at that time.

Whether or not Dr. Godfrey wins national acclaim, he will for a year wear the State mantle and like his predecessors (Dr. Elmer S. Bagnall, the late Dr. Dean Sherwood Luce, who was the country's General Practitioner of the Year in 1951, Dr. James G. Simmons and Dr. Harvey A. Kelly) represent to the public all that is specific and general in the general practice of medicine.

And Dr. Godfrey will wear his mantle well, for according to his confreres of the Charles River District "in his medical practice, his community activities, and in his contributions to the activities of his district and state societies, he epitomizes the ideal qualities of the general practitioner of today and yesterday."

The announcement of his nomination will precipitate a flock of congratulatory messages from friends

old and new. Perhaps for the first time, Dr. Godfrey will realize that the many friends he has made and served since he began the practice of medicine in 1908 have not forgotten him and that by his selection of general medicine he chose a rewarding career.

To the many messages that Dr. Godfrey, senior fellow, councilor and beloved physician, will receive, the *Journal* adds its heartiest congratulations.

1956 PRIZE-ESSAY COMPETITION

THE seventh student prize-essay competition, conducted by the *Journal* in 1955, was successful to the point that the number of essays submitted was appreciably greater than in any of the six previous years of the competition. The first prize was carried off by Milton Wigod, at the time a fourth-year student at the Medical College of Virginia. His paper, reporting a case of idiopathic pulmonary hemosiderosis, was published as a special article in the *Journal* of September 8, 1955.

Announcement is made that the eighth of these annual contests will close on March 15, 1956, on which date competing manuscripts must be in the hands of the editor.

As usual, the essay will consist of the report of a clinical case personally investigated by the student in the course of his or her academic work. The report is to be combined with a discussion of the pathologic condition represented by the case and a review of the important literature on the subject. It should follow the usual form of case reports as published in the *Journal*.

The usual terms of the competition will apply:

Manuscripts must be not more than 5000 words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be accompanied by a certification from the dean of the medical school concerned stating that the author is a member in good standing of the fourth-year class and specifying the expected date of graduation. No manuscripts will be returned.

A cash prize of $100 will be paid for the best essay of those found to be suitable for consideration, and the paper will be published in the *Journal* if the quality is considered to conform to the standards by which the editors usually judge material submitted; the author will receive a hundred free reprints. A second prize will consist of $25, and a third prize of a two-year subscription to the *Journal*. The editors reserve the right to withhold the awarding of any prizes if no papers of sufficient merit are submitted.

It is emphasized that in establishing this competition the editors are interested as much in encouraging good medical writing as in promoting the collection of scientific and clinical material. Particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

Medical Lectures of Harvard University. — *The Introductory Lecture will be delivered at the Massachusetts Medical College, on Wednesday, Nov. 7th, at 12 o'clock, by Professor Storer. Physicians, and gentlemen interested in Medical Science, are respectfully invited to attend.*

Boston M. & S. J., *Nov. 1, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

USSHER — Clarence D. Ussher, M.D., died on September 20, in Santa Monica, California. He was in his eighty-sixth year.

Dr. Ussher received his degree from the University Medical College of Kansas City in 1896.

He is survived by his widow, one daughter and three sons.

SOCIAL SECURITY — THE BIG ISSUE

To the Secretary: Coming is the biggest issue to face the medical profession since the defeat of socialized medicine: the extension of compulsory social security.

Although the American Medical Association has done all in its power to defeat this issue, and has been successful to date, we find that very few doctors actually know what it is all about, how it will affect them, the good and bad features of it, and why the American Medical Association has opposed it.

Social Security first came into being in the United States in the depression year of 1935 and has been insidiously growing ever since. The last group left to conquer is the medical profession, and the time is now ripe.

Soon after Congress reconvenes in January, the Senate will be asked to vote on a new facet for Old Age and Survivor's Insurance — the "Permanent Disability Clause," which has already passed the House of Representatives.

This new clause will take permanent and total disability benefits out of Public Assistance and place them under Old Age and Survivor's Insurance, where they will no longer require a Needs Test.

The bad feature of this clause lies in the fact that the physician will be called upon to determine and pass on the question whether or not a permanent and total disability exists. Thus legislation compromises the physician in many ways, he and his patient being forced into the extension of the Welfare State and an undoubted increase in taxes!

Some of the acceptable features of the program are as follows:

1. If a physician is employed, the premium is

partly paid by his employer. He also is more apt to retire and at the age of sixty-five will be eligible for social-security benefits provided he does not earn more than $1,200 a year.

2. If he died young, his wife would be eligible for benefits, the amount varying with the number of dependents. For example, a widow and one child could receive $162.80 a month; a widow with more than one child could receive $200.00 a month until the children became eighteen years of age.
3. If the physician retired at the age of sixty-five, he could receive $98.50 a month. When his wife reached sixty-five the two would receive $147.80 a month. (It should be noted that benefits are to be increased on July 1, 1956.)

Some of the reasons why the American Medical Association and physicians have opposed inclusion in Old Age and Survivor's Insurance are as follows:

1. Like socialized medicine, Old Age and Survivor's Insurance is compulsory legislation and smacks of adulterated Marxism.
2. The physician, unlike the majority of the population, is self employed and would pay into the system twice the amount that workers do.
3. Its financial soundness is questioned, since it has been estimated that this Old Age and Survivor's trust fund should have currently $250,000,000,000 in reserves instead of the $20,000,000,000 it does contain. It is placing unburdenable tax loads on our children and the citizens of the future.
4. Many today are receiving "windfall benefits" — benefits that are out of proportion to the amount that they have paid in. Senior citizens of today are receiving bargains, but these bargains will not long be available.
5. The manner in which the funds are received and used for current governmental expenses by converting them into future due bonds is also questioned.
6. The future deficit the plan now has and will incur can only be balanced by unpalatable taxes in the future.
7. Old Age and Survivor's Insurance is not insurance but a disguised program of old-age assistance or mass charity without a *means test*. For example, there is a decreasing relation between the amount of social-security taxes and its benefits; there is no contract between the insurer and the insured (Congress can and does change the program at will); there is no loan or surrender value; and when eligible persons aged sixty-five to seventy-two earn more than $1,200 their benefits are reduced proportionately to nothing.
8. The only way to postpone the day of reckoning for some time to come is to force into the scheme persons who are not apt to use many benefits. Physicians and other self-employed persons are the prime candidates for inclusion in this bailing-out process.

Statistics show that 13,000 physicians in general practice are over sixty-five, which is the conventional age for retirement. Eight of every 10 physicians over sixty-five are still in active practice. One of every 2 in the group sees more than 40 patients in an average week. One of every 4 treats patients of all ages. One of every 4 will handle all types of cases. Three of every 4 do not accept surgical cases.

It seems clear, however, that the majority of the physicians over sixty-five remain important members of the health teams of their communities.

This is an important issue; it requires study and action by every physician. The bill has already passed the House of Representatives. In January it goes to the Senate, and unless the American Medical Association has the support of every member, exerting his influence on his senators, it faces certain enactment.

It has been voted by the Executive Council of the Society that the district societies poll their membership and record their vote with the State Society. This is necessary to find out how the medical profession stands on this issue.

It is requested that all who desire that this issue be defeated get in touch with their senators, by mail or by telegram, or, wherever possible, by personal contact, *Now*.

A complete history of the growth of social security is embodied in the report of the Committee on National Legislation, which has been reprinted from the *Circular of Advance Information* and sent to every fellow of the Society. No fellow of the Society should fail to read it.

NICHOLAS S. SCARCELLO, M.D.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE		CLINIC CONSULTANT
Gardner	November	1	Carter R. Rowe, M.D.
Haverhill	November	2	William T. Green, M.D.
Greenfield	November	3	Charles L. Sturdevant, M.D.
Lowell	November	4	Albert H. Brewster, M.D.
Salem	November	7	Paul W. Hugenberger, M.D.
Brockton	November	10	George W. Van Gorder, M.D.
Lynn*	November	14	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Pittsfield	November	16	Edward J. Coughlin, Jr., M.D.
Hyannis	November	17	Paul L. Norton, M.D.
Worcester	November	18	John W. O'Meara, M.D.
Springfield	November	22	James D. Fisher, M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

Fall River November 28 David S. Grice, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	November 1, 8, 15, 22, 29
Fitchburg	November 2, 9, 16, 23, 30

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

LOANS FOR PRACTICE IN RURAL AND SUBURBAN AREAS

To the Editor: The Sears Foundation and the American Medical Association have joined in a plan to help physicians establish themselves in rural or rapidly expanding suburban communities. Physicians who have just completed their training or returned from military service often have insufficient funds or resources to purchase equipment or furnish offices.

The plan allows for unsecured, low-cost, ten-year loans of up to $25,000 to physicians seeking to establish new practices but unable to arrange full local financing. It requires also that the application indicate a need for a practice in the proposed locality and for good success and public service, and that he give evidence of effort and thought in planning a well organized, effective practice unit. The plan stimulates early repayment of the loans, and contributions made by the grantee will be turned back into the fund for the establishment of more units.

The aim is to realize the principles of opportunity, incentive, mutual help and self-reliance, and to give the American people the best possible medical care. It relies on individual initiative and enterprise, and is sustained entirely by those who benefit from it.

Booklets describing the methods of the plan will be in the offices of every state medical society and at the headquarters of the American Medical Association, and can be borrowed for inspection. Applications should be sent to the regional office of the Sears-Roebuck system, which, for New England, New York, Pennsylvania, Maryland, Delaware and West Virginia, is at Philadelphia 32, Pennsylvania (c/o H. K. Duffield).

This plan has the full approval of the trustees of the American Medical Association, is supervised in its medical aspects by an advisory board of members drawn from the House of Delegates, and has very favorable possibilities.

Lawrence R. Dame, M.D.

Greenfield, Massachusetts

BOOK REVIEW

Regional Allergy of the United States, Canada, Mexico and Cuba. Edited by Max Samter, M.D., and Oren C. Durham. 8°, cloth, 395 pp., with illustrations and tables. Springfield, Illinois: Charles C Thomas, 1955. $8.50.

The basic problems of allergy appear to be the same no matter where they occur. The causes of many allergic syndromes vary greatly from region to region. How does the allergist answer the patient who asks if a move to Kansas will affect his hay fever or bronchial asthma? Until recently, the answer could be found only in the individual pollen and mold surveys done by members of the American College of Allergists, the American Academy of Allergy and interested nonmedical botanists — for example, Roger Wodehouse and Oren Durham.

In the present monograph, Dr. Max Samter and Dr. Oren C. Durham have called upon 39 collaborators to list the geography, the climate and the allergenic factors present in their respective areas. Each is an outstanding expert in his field. With coverage of eastern Canada, New England and northern and eastern New York State and New York City, Buffalo and western New York, eastern Pennsylvania, New Jersey and Delaware, western Pennsylvania and West Virginia, eastern Ohio, Maryland, the South Atlantic states, Kentucky, Tennessee, Georgia, Florida and Cuba and Mexico, as well as the central states and the western states, almost all parts of the country are adequately described. For ragweed pollen, the table lists the states and the counts for individual cities.

In these days, when practically everybody travels, this book is indispensable for the internist practicing allergy. Any physician who has allergic patients will find its information invaluable.

Ethan Allen Brown, M.D.

NOTICES

ANNOUNCEMENTS

Dr. David Landau wishes to announce a change of office from 31 Bay State Road, Boston, to 350 Beacon Street, Boston. The telephone number will remain unchanged.

Dr. Bernard Lown announces the opening of an office for the practice of internal medicine and cardiology at 416 Marlboro Street, Boston, Massachusetts.

Dr. Ben Selling, in association with Dr. Samuel L. Gargill, announces the opening of an office for the practice of internal medicine at 474 Beacon Street, Boston 15, Massachusetts.

MASSACHUSETTS HEART ASSOCIATION

The Kidney Section of the Massachusetts Heart Association will hold a meeting at the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, November 7, at 8 p.m.

Dr. Henry L. Barnett will talk on "Nephrosis in Children." Physicians and medical students are invited.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The thirty-fifth annual meeting of the Association for Research in Nervous and Mental Disease will be held at the Hotel Roosevelt, New York City, December 9 and 10, 1955.

The subject of the meeting will be "The Neurologic and Psychiatric Aspects of the Disorders of Aging."

YALE UNIVERSITY SCHOOL OF MEDICINE

The first children's tumor clinic in Connecticut has been established at the Yale-New Haven Medical Center. The clinic is sponsored by the Yale School of Medicine, the Grace-New Haven Community Hospital and the Connecticut Division of the American Cancer Society.

Dr. David H. Clements and Dr. Alan Merman will be directors of the clinic.

INTER-SOCIETY CYTOLOGY COUNCIL

The annual scientific meeting of the Inter-Society Cytology Council will be held at the Hotel Statler, Cleveland, Ohio, November 11 and 12.

The program, which will consist of papers presented in four general sessions, is as follows:

New Advances in Cytology.
Applied Cytology.
Round-Table Discussions.
Symposium: Problem of early endometrial cancer.

All physicians, medical students and technicians interested in cytology are invited to attend. Further information may be obtained from Dr. Paul F. Fletcher, Secretary-Treasurer, Inter-Society Cytology Council, 634 North Grand Boulevard, St. Louis 3, Missouri.

FIFTH PANAMERICAN CONGRESS OF GASTROENTEROLOGY

The fifth Panamerican Congress of Gastroenterology and the sixth annual meeting of the Sociedad Cubana de Gastroenterologia will be held in Havana, January 20 through 27. The Congress will be preceded by the meeting. Official languages of the Congress will be Spanish, English and Portuguese.

Further information concerning the Congress may be obtained from Dr. Eduardo Frejomil, P. O. Box 2562, Habana, Cuba.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 1. Boston City Hospital House Officers' Association. Page 577, issue of September 29.

NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

NOVEMBER 1–30. Consultation Clinic for Crippled Children in Massachusetts. Page 744, issue of October 27.

NOVEMBER 2. New England Conference on Allergy and Related Subjects. Page 667, issue of October 13.

NOVEMBER 2–5. American Society of Tropical Medicine and Hygiene. Page 624, issue of October 6.

NOVEMBER 2, 1955–MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 7. Massachusetts Heart Association. Page 745, issue of October 27.

NOVEMBER 7 and DECEMBER 5, 1955, and JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

NOVEMBER 7, 21 and DECEMBER 5, 1955, and JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

NOVEMBER 8. Harvard Medical Society. Page 708, issue of October 20.

NOVEMBER 10–12. American College of Cardiology. Page 394, issue of September 1.

NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 745.

NOVEMBER 14 and 18. American Public Health Association. Page 578, issue of September 29.

NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 17 and DECEMBER 15. Arthritis Study Unit. Page 668, issue of October 13.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.

NOVEMBER 30, 1955, and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

DECEMBER 5–14, 1955, and JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

DECEMBER 7, 1955, and JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 6.

DECEMBER 9 and 10. Association for Research in Nervous and Mental Diseases. Page 745, issue of October 27.

DECEMBER 14, 1955, and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Notice above.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 3

THURSDAY, NOVEMBER 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m.–12:00 m. Thoracic Conference. Chemotherapy of Tuberculosis. Dr. Stanton T. Allison. Amphitheater, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, NOVEMBER 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*7:30–9:30 p.m. Postgraduate Medical Institute. Treatment of Kidney Disorders in Adults. Drs. Aisner and Relman. Holyoke Soldiers' Home, Holyoke.

SATURDAY, NOVEMBER 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Ettsen and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–10:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Drs. MacMahon and Baty. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Mortality and Morbidity. Dr. Orr. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*8:30 p.m. Fried Lecture Series. Fat Metabolism and Hypercholesteremia. Dr. William R. Waddell. Usen Auditorium, Newton-Wellesley Hospital.

TUESDAY, NOVEMBER 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*4:00–5:00 p.m. Surgical Pathological Conference. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Ettsen and staff. Stearns Auditorium, New England Center Hospital.
*5:15 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
8:00 p.m. Harvard Medical Society. Symposium on Poliomyelitis. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

WEDNESDAY, NOVEMBER 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.

(Concluded on page xx)